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THE HARVEY LECTURES

DELIVERED UNDER THE AUSPICES OF

THE HARVEY SOCIETY OF NEW YORK

UNDER THE PATRONAGE OF THE NEW YORK ACADEMY OF MEDICINE

1920-1921

BY

DR. JACQUES LOEB
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SERIES XVI

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PREFACE

THE Lectures of the Harvey Society have become so well recognized and occupy such a prominent place in medical literature that prefatory remarks are superfluous. The intention of the founders of the Society was to have each year a series of contributions each one of which was to bring to date the particular subject under discussion. The various lecturers have appreciated this object, and thus helped to make continuous a definite policy.

The secretary takes pleasure in acknowledging the kindness of the editors of various journals for permission to reprint the following lectures: Science, for the lecture of Dr. Loeb; Journal of the American Medical Association for the lectures of Dr. Hess and Dr. Foster; Archives of Internal Medicine for the lecture of Dr. Wiggers; the American Journal of Medical Science for the lecture of Dr. Richards; and the Quarterly Publication of the American Statistical Association for the lecture of Sir Arthur Newsholme.

HOMER F. SWIFT, *Secretary.*

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A SOCIETY FOR THE DIFFUSION OF KNOWLEDGE OF THE MEDICAL SCIENCES

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I.

This Society shall be named the Harvey Society.

II.

The object of this Society shall be the diffusion of scientific knowledge in selected chapters in anatomy, physiology, pathology, bacteriology, pharmacology, and physiological and pathological chemistry, through the medium of public lectures by men who are workers in the subjects presented.

III.

The members of the Society shall constitute three classes: Active, Associate, and Honorary members. Active members shall be laboratory workers in the medical or biological sciences, residing in the City of New York, who have personally contributed to the advancement of these sciences. Associate members shall be meritorious physicians who are in sympathy with the objects of the Society, residing in the City of New York. Members who leave New York to reside elsewhere may retain their membership. Honorary members shall be those who have delivered lectures before the Society and who are neither active nor associate members. Associate and honorary members shall not be eligible to office, nor shall they be entitled to a vote.

Members shall be elected by ballot. They shall be nominated to the Executive Committee and the names of the nominees shall accompany the notice of the meeting at which the vote for their election will be taken.

CONSTITUTION

IV.

The management of the Society shall be vested in an executive committee, to consist of a President, a Vice-President, a Secretary, a Treasurer, and three other members, these officers to be elected by ballot at each annual meeting of the Society to serve one year.

V.

The Annual meeting of the Society shall be held soon after the concluding lecture of the course given during the year, at a time and place to be determined by the Executive Committee. Special meetings may be held at such times and places as the Executive Committee may determine. At all the meetings *ten* members shall constitute a quorum.

VI.

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THE PROTEINS AND COLLOIDAL CHEMISTRY*

DR. JACQUES LOEB

Rockefeller Institute for Medical Research

I

THE proteins, like certain other constituents of protoplasm, are colloidal in character, *i. e.,* they are not able to diffuse through animal membranes which are permeable to crystalloids. For this reason a number of authors have tried to explain the behavior of proteins from the viewpoint of the newer concepts of colloid chemistry. Foremost among these concepts is the idea that the reactions between colloids and other bodies are not determined by the purely chemical forces of primary or secondary valency but follow the rules of "adsorption." Although a number of authors, during the last twenty years, *e.g.,* Bugarszky and Liebermann, Hardy, Pauli, Robertson, Sörenson, and others, have advocated a chemical conception of the reactions of proteins, their experiments failed to convince the other side since these experiments could just as well be explained on the basis of the adsorption theory. There were two reasons for this failure: First, the experiments did not show that ions combined with proteins in the typical ratio in which the same ions combine with crystalloids. This proof only became possible when it was recognized that the hydrogen ion concentration of the protein solution determines the amount of ion entering into combination with a protein, and that therefore the ratios in which different ions combine with proteins must be compared for the same hydrogen ion concentrations. Since the former workers were in the habit of comparing the effects of the same quantities of acid or alkali

*Delivered October 16, 1920.

The writer's experiments, on which this address is based, have appeared in the *J. Gen. Physiol.*, 1918-19, I., 39, 237, 363, 483, 559; 1919-20, II.; 87; 1920-21, III., 85.

added instead of comparing the behavior of proteins at the same hydrogen ion concentration they were not able to furnish the final proof for the purely chemical character of the combination between ions and proteins, and nothing prevented chemists from assuming that proteins formed only adsorption compounds with acids, bases, and neutral salts.

The second reason for the failure to prove the purely chemical character of the protein compounds lay in the so-called Hofmeister series of ion effects. Hofmeister was the first to investigate the effects of different salts on the physical properties of proteins, and he and his followers observed that the relative effects of anions on the precipitation, the swelling, and other properties of proteins were very definite and that the anions could be arranged in definite series according to their relative efficiency, the order being independent of the nature of the cation. Similar series were also found for the cations, though these series seemed to be less definite. These Hofmeister series were a puzzle inasmuch as it was impossible to discover in them any relation to the typical combining ratios of the ions, and this lack of chemical character in the Hofmeister series induced chemists to explain these series on the assumption of a selective adsorption of these ions by the colloids.

To illustrate this we will quote the order which, according to Pauli, represents the relative efficiency of different acids on the viscosity of blood albumin,

HCl > monochloracetic > oxalic > dichloracetic < citric < acetic > sulfuric > trichloracetic acid,

where HCl increased the viscosity most and trichloracetic or sulfuric least. In this series the strong monobasic acid HCl is followed by the weak monochloracetic acid, this is followed by the dibasic oxalic acid; later follows the weak tribasic citric acid, then the very weak monobasic acetic acid, then the strong dibasic sulfuric acid, and finally again a monobasic acid, trichloracetic. Pauli is a believer in the chemical theory of the behavior of proteins but it is impossible to harmonize his series of anions with any purely chemical theory of the behavior of proteins.

The ion series of Hofmeister are no more favorable for a

chemical conception. Thus, according to Hofmeister, gelatin swells more in chlorides, bromides and nitrates than in water, while in acetates, tartrates, citrates or sugar it swells less than in water. R. Lillie arranges ions according to their depressing effect on the osmotic pressure of gelatin solution in the following way,

$$Cl > SO_4 > NO_3 > Br > I > CNS.$$

These series again betray no relation to the stoichiometrical properties of the ions. As long as these Hofmeister series were believed to have a real existence it seemed futile to decide for or against a purely chemical theory of the behavior of colloids since even with a bias in favor of a chemical theory the Hofmeister series remained a puzzle.

The writer believes to have removed these difficulties by using protein solutions of the same hydrogen ion concentration as the standard of comparison. In this way he was able to show that acids, alkalies, and neutral salts combine with proteins by the same chemical forces of primary valency by which they combine with crystalloids, and that, moreover, the influence of the different ions upon the physical properties of proteins can be predicted from the general combining ratios of these ions. The so-called Hofmeister series have no real existence, being the result of the fact that the older workers failed to measure the most important variable in the case, namely the hydrogen ion concentration of their protein solutions, a failure for which they can not be blamed since the methods were not sufficiently developed.

II

Pauli and a number of other workers assume that both ions of a neutral salt are adsorbed simultaneously by non-ionized protein molecules. If we consider the hydrogen ion concentration of the proteins we can show that only the cation or only the anion or that neither ion can combine at one time with a protein; and that it depends solely on the hydrogen ion concentration of the solution which of the three possibilities exists.

Proteins exist in three states, defined by their hydrogen ion concentration, namely, (*a*) as non-ionogenic or isoelectric protein,

(*b*) metal proteinate (*e. g.*, Na or Ca proteinate), and (*c*) protein-acid salts (*e. g.*, protein chloride, protein sulfate, etc.). We will use gelatin as an illustration. At one definite hydrogen ion concentration, namely $10^{-4.7}$ N (or in Sörensen's logarithmic symbol at pH=4.7), gelatin can combine practically with neither anion not cation of an electrolyte. At a pH>4.7 it can combine only with cations (forming metal gelatinate, *e.g.*, Na gelatinate), at a pH<4.7 it combines with anions (forming gelatin chloride, etc.). This was proved in the following way: Doses of 1 gm. of finely powdered commercial gelatin (going through sieve 60 but not through 80), which happened to have a pH of 7.0, were brought to a different hydrogen ion concentration by putting them for 1 hour at about 15° C. into 100 c.c. of HNO_3 solutions varying in concentration from M/8192 to M/8. After this they were put on a filter, the acid being allowed to drain off, and were washed once or twice with 25 c.c. of cold water (of 5° C. or less) to remove remnants of the acid between the granules of the powdered gelatin. These different doses of 1 gm. of gelatin now possessing a different pH were all put for 1 hour into beakers containing the same concentration, *e. g.*, M/64, of silver nitrate at a temperature of 15°C. They were then put on a filter and washed 6 or 8 times each with 25 c.c. of ice cold water; the wash water must be cold since otherwise the particles will coalesce and the washing will be incomplete. This washing serves the purpose of removing the $AgNO_3$ held in solution between the granules, thus allowing us to ascertain where the Ag is in combination with gelatin and where it is not in combination, since the Ag not in combination with gelatin can be removed by the washing while the former can not, or at least only extremely slowly by altering the pH. After having removed the $AgNO_3$ not in combination with gelatin by washing with ice cold water we melt the gelatin by heating to 40° C., adding enough distilled water to bring the volume of each to 100 c.c., determine the pH of each solution potentiometrically or colorimetrically, and expose the solutions in test-tubes to light, the previous manipulations having been carried out in a dark room (with the exception of the determination of pH,

for which only part of the gelatin solution was used). In 20 minutes all the gelatin solutions with a pH>4.7, *i.e.*, from pH 4.8 and above, become opaque and then black, while all the solutions of pH<4.7,*i.e.*, from 4.6 and below, remain transparent even when exposed to light for months or years. The solutions of pH 4.7 become opaque, but remain white, no matter how long they may have been exposed to light. At this pH—the isoelectric point—gelatin is not in combination with Ag, but it is insoluble. Hence the cation Ag is only in chemical combination with gelatin when the pH is>4.7. At pH 4.7 or below gelatin is not able to combine with Ag ionogenically. This statement was confirmed by volumetric analysis.

The same tests can be made for any other cation the presence of which can be easily demonstrated. Thus when powdered gelatin of different pH is treated with $NiCl_2$ and the $NiCl_2$ not in combination with gelatin be removed by washing with ice cold water, the presence of Ni can be demonstrated in all gelatin solutions with a pH>4.7 by using dimethylglyoxime as an indicator. All gelatin solutions of pH of 4.8 or above assume a crimson color upon the addition of dimethylglyoxime, while all the others remain colorless. When we treat gelatin with copper acetate, and wash afterwards, the gelatin is blue and opaque when its pH is 4.8 or above, but is colorless and clear for pH<4.7. Most striking are the results with basic dyes, *e. g.*, basic fuchsin or neutral red, after sufficient washing with cold water; only those gelatin solutions are red whose pH is above 4.7, while the others are colorless.

On the acid side of the isoelectric point, *i.e.*, at pH<4.7, the gelatin is in combination with the anion of the salt used. This can be demonstrated in the same way by bringing different doses of powdered gelatin to different pH and treating them for one hour with a weak solution of a salt whose anion easily betrays itself, *e. g.*, M/128 $K_4Fe(CN)_6$. If after this treatment the powdered gelatin is washed six times with cold water to remove the $Fe(CN)_6$ not in chemical combination with gelatin and if 1 per cent. solutions of these different samples of gelatin are made, it is found that when the pH is<4.7 the gelatin solution turns blue after a few days (due to the formation of ferric salt), while

solutions of gelatin with a pH of 4.7 or above remain permanently colorless. Hence gelatin enters into chemical combination with the anion $Fe(CN)_6$ only when pH is <4.7. The same can be demonstrated through the addition of ferric salt when gelatin has been treated with NaCNS, the anion CNS being in combination with gelatin only where the pH is <4.7. Acid dyes, like acid fuchsin, combine with gelatin only when pH is <4.7.

In this way it can be shown that when the pH is <4.7 gelatin can combine only with cations; when the pH is >4.7 gelatin can combine only with anions, while at pH 4.7 (the isoelectric point) it can combine with neither anion nor cation. The idea that both ions influence a protein simultaneously is no longer tenable.

It also follows that a protein solution is not adequately defined by its concentration of protein but that the hydrogen ion concentration must also be known, since each protein occurs in three different forms—possibly isomers—according to its hydrogen ion concentration.

In the experiments just discussed it was necessary to wash the powdered gelatin to find out at which pH an ion was in combination with the gelatin. This has led some authors to the belief that in all my experiments the washing was a necessary part of the procedure. I therefore will call especial attention to the fact that the experiments to be described in the rest of the paper were carried out with isoelectric gelatin to which just enough acid or alkali was added to bring it to the hydrogen ion concentration required for the purpose of the experiment.

III

When a protein is in a salt solution, *e. g.*, NaCl, it will combine with Na forming sodium proteinate as soon as the pH is higher than the isoelectric point of the protein; when, however, the pH falls below that of the isoelectric point of the protein the Na is given off and protein chloride is formed.

Moreover, the writer has been able to show by volumetric analysis that the quantity of anion or cation in combination with the protein is an unequivocal function of the pH. When we add HCl to isoelectric gelatin and determine the pH we always find

the same amount of Cl in combination with a given mass of originally isoelectric gelatin for the same pH; so that if we know the pH and the concentration of originally isoelectric gelatin present we can also tell how much Cl is in combination with the protein for this pH. The same is true when we add an alkali to the isoelectric gelatin. For the same pH the amount of cation in combination is always the same. These facts have led the writer to propose the following theory. When we add an acid, *e. g.*, HCl, to isoelectric gelatin (or any other isoelectric protein) an equilibrium is established between free HCl, protein chloride, and non-ionogenic or isoelectric protein; when we add alkali an equilibrium is established between metal proteinate, non-ionized protein, and the hydrogen ions. Sörensen was led to a similar view on the basis of entirely different experiments.

IV

This fact that the hydrogen ion concentration of a protein solution determines the quantity of protein salt formed is the basis on which the following proof for the purely chemical character of the combination between proteins and other bodies rests. The experiments mentioned thus far in this paper do not yet allow us to decide whether the ions are "adsorbed" or in chemical combination with the proteins. We will now show that acids and bases combine with proteins in the same way as they combine with crystalline compounds, namely by the purely chemical forces of primary valency. The combination between acids and proteins, is analogous to that between acids and NH_3, and the combination between bases and proteins is analogous to that between CH_3COOH and an alkali. This can be proved in the following way. We know that a weak dibasic or tribasic acid gives off one hydrogen ion more readily than both or all three; while in a strong dibasic acid, like H_2SO_4, both hydrogen ions are held with a sufficiently small electrostatic force to be easily removed. If the forces which determine the reaction between these acids and proteins are purely chemical it would follow that three times as many c.c. of 0.1N H_3PO_4 are required to bring 100 c.c. of 1 per cent. solution of isoelectric gelatin to

a given pH, *e. g.*, 3.0, as are required in the case of HNO_3 or HCl; while twice as many c.c. of 0.1N oxalic as of HNO_3 should be required. On the other hand, it should require just as many c.c.

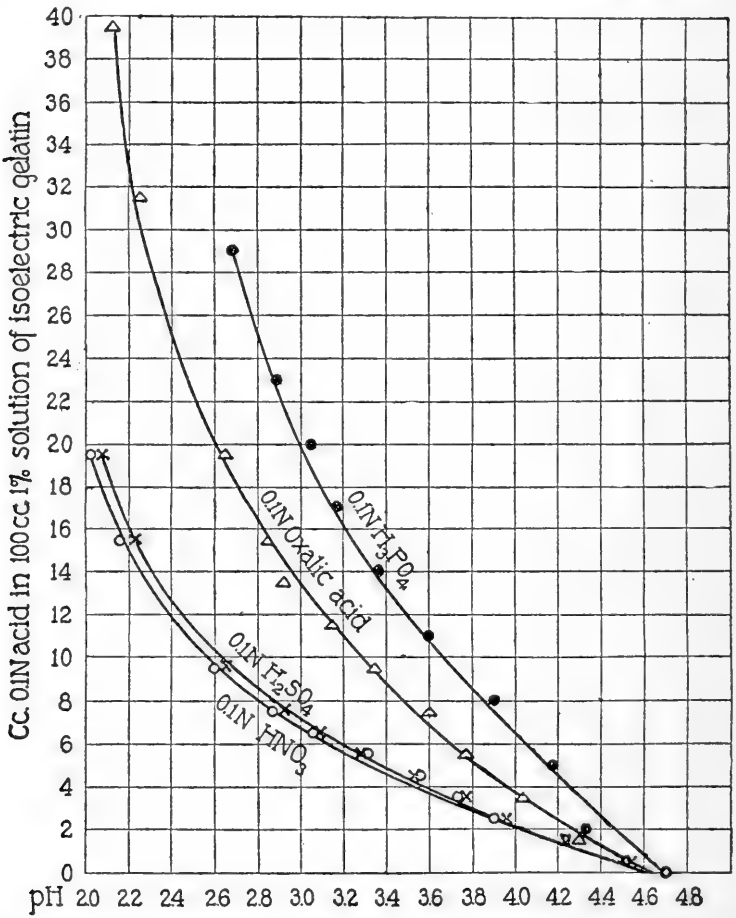


FIG. I.—The ordinates represent the c.c. of 0.1 N acid in 100 c.c. of 1 per cent. solution of isoelectric gelatin required to bring the solution to the pH indicated in the abscissæ. The curves for 0.1 N H_2SO_4 and 0.1 HNO_3 are identical while the values for H_3PO_4 and oxalic acid differ, being approximately in the ratio of HNO_3: oxalic acid: H_3PO_4 as 1:2:3.

of 0.1N H_2SO_4 as HNO_3. Fig. 1 shows that this is the case. The ordinates of this figure are the c.c. of 0.1 N acid required to bring 1 gm. of isoelectric gelatin to the pH indicated in the abscissæ

by the four acids mentioned, namely HNO_3, H_2SO_4, oxalic, and phosphoric acids. The curves for H_2SO_4 and HNO_3 are identical while, for the same pH, the value for H_3PO_4 is always approximately three times and the value for oxalic acid is always approximately twice as high as for HNO_3.

On the basis of the same reasoning as applied to acids we should expect that equal numbers of c.c. of 0.1 N $Ca(OH)_2$ and $Ba(OH)_2$ as of LiOH, NaOH, and KOH should be required to bring 100 c.c. of a 1 per cent. solution of isoelectric gelatin to the same pH, and the writer was able to show that this is the case.

TABLE I

C.c. of 0.01 N Acid in Combination with 10 c.c. of a 1 Per Cent. Gelatin Solution at Different pH

pH	3.1	3.2	3.3	3.4	3.5	3.7	3.9	4.1	4.2	4.3
HNO_3 ...	4.35	4.1	3.6	3.2	2.85	2.45	1.9	1.45		0.75
Oxalic acid	9.6	8.75	7.6	6.7	6.00	4.3	3.0		1.65	
H_3PO_4 ...		12.4	10.4	9.8	9.00	7.4	5.8	4.5	2.6	2.1

Similar results were obtained with crystalline egg albumin.

When we have a solution of a gelatin-acid salt of originally 1 per cent. isoelectric gelatin and of a certain pH, *e. g.*, 3.0, we have free acid in the solution and a certain amount of the anion of the acid in combination with gelatin. We can find out by volumetric analysis how much of the anion is in combination with the protein by making certain corrections discussed in former papers. In this way it can also be ascertained that all weak dibasic acids combine in molecular proportions with isoelectric protein, while strong dibasic acids and diacidic alkalies combine in equivalent proportions with proteins, as is shown by Table I. It follows from this table that for the same pH the amount of HNO_3, oxalic, and phosphoric acids in combination with the same quantity of originally isoelectric gelatin is always in the proportion of 1 :2 :3.

We can therefore state that the ratios in which ions combine with proteins are identical with the ratios in which the same ions

combine with crystalloids. Or in other words, the forces by which gelatin and egg albumin (and probably proteins in general) combine with acids or alkalies are the purely chemical forces of primary valency.

V.

The most important fact for our purpose is that from the combining ratios just mentioned the influence of acids and bases on the physical properties of proteins can be predicted. This influence is altogether different from that stated in the so-called Hofmeister series of ions or by the ion series of Pauli and his collaborators, and this difference is due to the fact that these latter authors compared the effects of equal quantities of acids or alkalies while we found it necessary to compare the physical properties of solutions of proteins of the same hydrogen ion concentration. If this is done the following rule is found. All those acids whose anion combines as a monovalent ion raise the osmotic pressure, viscosity, swelling of protein about twice as much as the acids whose anion combines as a bivalent anion for the same pH. The same valency rule holds for the cations of different alkalies.

We have seen that at the same pH three times as many c.c. of 0.1 N H_3PO_4 as of HNO_3 are in combination with 1 gm. of originally isoelectric gelatin in 100 c.c. of solution. It follows from this that the anion of gelatin phosphate is the monovalent ion H_2PO_4 and not the trivalent anion PO_4. It follows likewise from the combining ratios discussed that the anion of oxalic acid in combination with protein is the monovalent anion HC_2O_4. The same is true for all weak dibasic or tribasic acids, namely that they combine with proteins forming protein salts with monovalent anion. It follows also from the combining ratios that the salt of a protein with a strong dibasic acid, as H_2SO_4, however, must have a divalent anion, *e. g.*, SO_4. If we compare the viscosity or osmotic pressure of 1 per cent. solutions of originally isoelectric gelatin with different acids of the same pH we find that these properties are identical for all gelatin salts with monovalent anion; in other words, 1 per cent. solutions of gelatin chloride,

bromide, nitrate, tartrate, succinate, citrate, or phosphate have all the same viscosity, and the same osmotic pressure at the same pH. The same is true for the swelling (Fig. 2). If we plot the curves for these three properties with pH as abscissæ and the

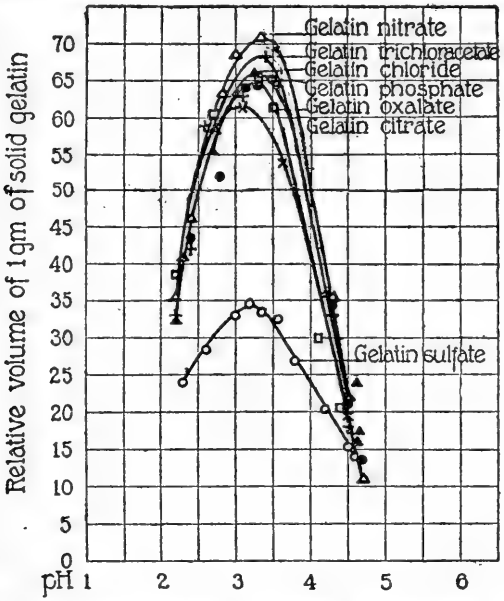


FIG. II.—Influence of different acids upon the swelling of gelatin when plotted over pH as abscissæ. The curves show that nitric, trichloracetic, hydrochloric, phosphoric, oxalic, and citric acids cause approximately the same degree of swelling, while sulfuric acid causes only about one half the amount of swelling. In the case of gelatin sulfate the anion is divalent; in the case of the other acids used it is monovalent. According to the Hofmeister series the curves for phosphate, oxalate and citrate should coincide with that of sulfate instead of coinciding with that of coloride.

values for osmotic pressure, viscosity, and swelling as ordinates, we get practically identical curves for gelatin chloride, bromide, nitrate, tartrate, succinate, citrate, and phosphate. The values for swelling are a minimum at pH 4.7 (the isoelectric point of gelatin) they rise rapidly with the fall of pH until they reach a maximum at pH about 3.2, and then they drop again. Each curve is the expression of an individual experiment. The maximum in the curves for gelatin chloride, bromide, nitrate, tartrate, succinate, citrate, and phosphate is practically identical, the variations between the values for these acids lying within the limit

of variation which we may expect if we plot six different experiments with the same acid. When, however, we plot the same curves for gelatin sulfate, we get curves which are considerably lower, reaching a height of only one half (or a little less than) those of gelatin-acid salts with monovalent anions. It may be of interest to compare our curves with those expected on the basis of Pauli's and Hofmeister's ion series. According to the latter theory the curves for phosphates, oxalates, citrates, and tartrates should be in the region of the SO_4 curve but not in the region of the Cl curve. Those authors who observed such differences did not measure the hydrogen ion concentration, attributing the effects due to the difference in the hydrogen ion concentration of their gelatin solutions erroneously to a difference in the anion effect. These elementary errors form the basis of a number of speculations current in biology and pathology.

When we compare monobasic acids of different strength, *e. g.*, acetic, mono-, di-, and trichloracetic acids, we find that the weaker the acid the more acid must be contained in a 1 per cent. solution of originally isoelectric gelatin to bring it to the same pH. If we compare the effect of these four acids on the osmotic pressure of gelatin we find that it is (within the limits of accuracy of these experiments) identical for the same pH. The curves for the influence of these four acids on the osmotic pressure of gelatin solution are practically identical when plotted over the pH as abscissæ; and, moreover, the curves are identical with the curves for HCl or H_3PO_4 in Fig. 1. The explanation of this fact is that at the same pH the same mass of originally isoelectric gelatin is in combination with the same quantity of these four acids and since the anions of these four acids are all monovalent the curves must be identical.

As far as the alkalies are concerned, we notice that the curve representing the effect of the weak base NH_4OH on the physical properties of proteins is the same as that for the strong bases LiOH, NaOH, KOH when plotted over pH as abscissæ, while the curves representing the effect of $Ca(OH)_2$ or $Ba(OH)_2$ on the same properties are considerably lower.

It is obvious that the valency of the ion in combination with

the protein has a noticeable influence on the properties of the protein salt formed, while the protein salts with ions of the same valency have all the same properties. The fact of the greatest importance is, however, that the influence of acids and bases on the physical properties of proteins is the expression of the combining ratios of the acids or bases with proteins so that we are able to predict the value of the physical properties from the combining ratios. This fact seems to give a final decision in favor of a purely chemical theory of these influences and against the colloidal theories as based on the Hofmeister or Pauli ion series.

The behavior of the proteins therefore contradicts the idea that the chemistry of colloids differs from the chemistry of crystalloids.

THE THEORIES OF BLOOD COAGULATION*

PROFESSOR JULES BORDET

Director of the Pasteur Institute of Brussels

FIRST of all, I beg you to excuse my imperfect knowledge of the English language and to accept my best thanks for the honor you have conferred upon me by inviting me to deliver the Harvey Lecture. I shall try to-night to give a brief resume of the chief theories which have been held concerning the mechanism underlying blood coagulation. This phenomenon deserves our interest, not only because of its physiological importance, but also as a striking example of the resources of experimental analysis. It can occur in vitro, and such is truly a very favorable condition for the success of investigation. Nevertheless, and although it has been the subject of innumerable researches, its mystery, up to the present time, has not been completely disclosed. You will not expect me to attempt a detailed review of the whole subject. I shall give only such broad outlines as will serve to make clear the modern conceptions which, seeming to afford the best explanation of this complicated process, especially deserve our attention.

I do not think it necessary to recall that coagulation is nothing else but the aggregation into meshes of fibrin of particles of fibrinogen, a substance which, as Fredericq showed forty-three years ago, preexists as a dispersed colloid in the circulating plasma. When the blood is shed from a wound, the first determining factor which, through successive modifications of the plasma, assures the solidification of fibrinogen, is, not infrequently, the mixture of the blood with very active principles liberated by the bruised tissue, or in other words, the addition to the blood of tissue extract. But such an influence is an additional one, foreign to the blood itself; and, limiting the problem, I

* Delivered October 30, 1920.

shall consider here, exclusively, the coagulation that blood is capable of showing solely by means of its own substances.

A most important, even decisive factor of this autonomic coagulation is the contact of a foreign solid body, which, such as glass, acts only physically by its presence, since it does not liberate any soluble substance. The contact, external factor, brings into activity the internal factors belonging to the blood, and that is the process through which the principle directly and immediately responsible for the coagulation, the fibrin-ferment or thrombin, is produced. In fact, the thrombin, which is found in large quantities in the clot or in the serum, does not exist, as Schmidt showed many years ago, in the circulating blood. Consequently, several stages are to be distinguished in the total process, the most important one being the period in which the thrombin appears; the fibrinogen itself playing merely a passive role. Fibrinogen can be extracted by special methods and obtained in a rather pure condition; but it must be kept in mind that the essential problem requiring the attention of the physiologist, is the coagulation, not of pure fibrinogen, but of the blood considered as a whole, that is, of a very complex medium, cellular and plasmatic, having a definite reaction and definite osmotic pressure, containing numerous constituents and especially colloids which presumably are apt to influence each other through molecular adhesion. Coagulation could not be studied without taking into consideration every influence apt to interfere in the phenomenon.

As a rule, the blood of mammalians clots promptly, and it was, therefore, essential to the success of investigation to find how the course of the process could be protracted and, moreover, how it could be stopped at the first period of its evolution, so as to make possible the separation of the cells from the still liquid plasma. Several methods have been devised in that direction; I shall only recall them briefly.

Concentrated salts, magnesium sulphate for instance, hinder the coagulation. Common salt, being a normal constituent of the organism, especially answers the purpose. Blood that has been salted at three or five per cent. immediately after

withdrawal from an artery yields by centrifugalization a clear plasma which does not clot so long as the high saline concentration is maintained, but which, diluted with distilled water added in sufficient proportion to reestablish the normal saline concentration, clots rather quickly. Decalcifying salts, the type of which is sodium oxalate, prevent wholly the coagulation, calcium salts being necessary to this phenomenon. By centrifugalization, a clear plasma is obtained, which is apt to clot when a calcium soluble salt, namely, chloride, is restored.

Coagulation is also prevented if, to the active contact of glass a contact is substituted which is not, if we may say so, felt by the blood or the plasma. A liquid does not feel a wall, I mean does not react physically to it, unless capable of adhering to it. Freund was the first to show that blood flowing from the artery does not clot, or at least clots very slowly, when received in a vessel the inside of which is coated with oil or vaseline. Paraffin, forming a solid coating, is very suitable to such experiments, and frequently permits the separation of the cells and the plasma by centrifugalization. I saw with Gengou that thus a clear plasma might be obtained and be kept fluid during twenty-four hours, but the clotting soon occurred when the plasma was brought into contact with glass. This experiment shows that the contact of glass can bring about its effect without any presence of cells, that is, without any vital interference; we have, therefore, to deal with a physicochemical phenomenon.

The blood of certain animals, namely, birds and fishes, as Delezenne has shown, clots very slowly by its own means, coagulation being greatly hastened by addition even of traces of tissue extract. Without the help of decalcification or of paraffin coating, the blood of a bird will keep fluid for a long time and even yield by centrifugalization a permanently liquid plasma, if the utmost care has been taken not to let the tube inserted into the vessel touch the wound, so as to prevent any trace of tissue extract mixing with the blood. As a matter of fact, this precaution ought to be taken regularly, whatever may be the species of animal under experiment, as it is quite a general rule that tissue extract accelerates the coagulation; this auxiliary

influence being particularly evidenced in the case of birds, because the avian blood is not so capable of spontaneous coagulation as is the blood of mammalians.

Thanks to such methods, the separation of the two constituents, cells and plasma, can be performed before any coagulation begins; and, let us emphatically insist upon this essential fact, before the appearance of any of the coagulating principle thrombin. There is no need to recall that serum yielded by coagulation contains thrombin.

We must now try to go further and subject plasma and cells to a closer analysis. Let us consider first the plasma. Soluble calcium salts are necessary to coagulation. How do they act? Pekelharing and Hammarsten have shown the essential fact that these salts are not necessary to the transformation of fibrinogen into fibrin under the influence of thrombin, but are indispensable to the formation of the latter, that is, to the production of thrombin from the mother-substances already present in the circulating blood. It is thus the production of thrombin which is prevented by the oxalate; but, on the other hand, the decalcification does not prevent the coagulation of fibrinogen by ready thrombin. Indeed, it has been proved that blood, oxalated immediately after withdrawal from the artery, remains permanently fluid, no thrombin being ever detected in it; whereas if serum yielded by normally clotted blood be oxalated, this oxalated serum, added to oxalated plasma, causes the coagulation of the latter. It follows from these facts that oxalated plasma is a most suitable reagent for the detection of thrombin in a given liquid; estimation of the coagulating power of such a liquid may then be made by taking into consideration the quantity of oxalated plasma a certain amount of this liquid is apt to coagulate, or the rapidity of the occurring coagulation. However, it must be borne in mind that, at least when present in serum, the activity of a given thrombin depends not only upon its quantity but also upon its age. The capacity of fresh serum to coagulate oxalated plasma decreases very quickly, by a spontaneous attenuation of the thrombin; and this fact affords a possibility of detecting whether a given thrombin has been produced quite recently or more

remotely. Several experiments, as we shall see, require such a determination.

Contact is also necessary for coagulation. How does it operate? I showed with Gengou many years ago that contact suggests the same remark as calcium does, that is, that contact with a foreign solid body (paraffin of course excepted) is necessary for the appearance of thrombin, but is not requisite for the coagulating influence of the latter. When blood is received in a paraffin vessel, thrombin is not formed; when received in a glass vessel, thrombin is produced in the zone of contact; which fact explains why coagulation begins along the wall. But when serum yielded by previously clotted plasma is added to blood or plasma kept in a paraffined vessel, the entire mass rapidly solidifies; the paraffin no longer exerting any inhibiting influence. This experiment explains why blood freshly extracted and placed in a glass vessel coagulates in a mass much more rapidly when shaken.

From whence does thrombin proceed? It does not exist as such in the circulating blood, although the latter contains everything requisite for its production. The circulating blood, therefore, contains the mother substance, or mother-substances, of thrombin, which for convenience may be called prothrombin, and which in the early stages of coagulation is converted into thrombin. What then is prothrombin?

Morawitz, sixteen years ago, made an important discovery concerning this subject. He found that if crushed tissue, muscular tissue for example, is added to serum yielded by normal coagulation, the coagulating power of this serum towards oxalated plasma considerably increases. And still, the extract of tissue by itself does not contain any thrombin, not being capable of coagulating oxalated plasma without the help of serum. We are, therefore, forced to conclude that the tissue extract contains something which is not thrombin, but which reacts with the serum so as to produce this active principle. Then the hypothesis at once presents itself that thrombin is derived from the interaction of two different substances: the one furnished by the tissue cells; the other by the serum. Undoubtedly, even before

the introduction of the tissue extract, a certain amount of thrombin existed in the serum; but it seems as if this fluid contained also an excess of the mother substance, the latter being capable of reacting with the tissue extract so as to generate a fresh supply of thrombin.

But the question immediately arises whether such an assumption, deduced from experiments in which tissue extract plays an important role, may be without any further inquiry applied to the autonomic coagulation of pure blood. As a matter of fact, it must be kept in mind that when injected into the circulation, the tissue extracts are highly toxic and cause sudden death due to intravascular coagulation. Undoubtedly, they contain some coagulating principle foreign to the blood itself. Because our task tonight is chiefly the study of the coagulation of pure blood, I shall dispense with discussing very fully the nature of this principle; it is probably an albuminoid substance and is markedly thermolabil, found specially in the tissues and not in the blood; and cannot be considered as a real mother substance of thrombin. But we must immediately add that, beside this peculiar principle, the tissue cells nevertheless contain one of the two mother-substances of thrombin, which exists also in the blood cells, is of a lipoid nature and may receive the name of cytozym. The other mother-substance, called by us serozym, is furnished by the blood fluid and is present in the serum. But we have naturally to inquire how these conceptions have arisen.

The assumption that the blood cells furnish one of the mother substances of thrombin is in perfect accordance with the results of experiments concerning the part played by those cells and chiefly by platelets in the coagulation. Platelets can be easily separated by a short centrifugalization of oxalated blood at a moderate speed; being very light, they remain in suspension whereas red and white corpuscles are deposited; the turbid supernatant fluid pipetted off is very rich in platelets. Now if such a platelet-plasma is centrifugalized a long time at a very high speed, the platelets finally are sedimented and a clear plasma may be obtained from which the platelets have not been thoroughly eliminated,—this being impossible,—but in which they

are present only in small number. Comparing these two plasmas, the one very rich, the other very poor in platelets, Lesourd and Pagniez found that by recalcification the former clots rapidly, the latter slowly. Delange and I completed these experiments by comparing the coagulating influence, on oxalated plasma, of the two sera thus obtained, or in other words, by comparing the amount of thrombin they contain, and found that serum yielded by the coagulation of plasma rich in platelets contains a much larger quantity of thrombin than is found in serum yielded by plasma poor in platelets. Consequently, the platelets actively participate in the production of the coagulating principle. This fact can be proved more distinctly still by the following experiment: a sediment constituted exclusively of these small cells is obtained by vigorously centrifugalizing oxalated plasma, previously carefully freed of its red and white corpuscles, but containing still its platelets. This platelet deposit, thoroughly washed, is emulsified in physiological solution, and one drop of the turbid emulsion thus obtained is added to a certain quantity of a serum which, having been obtained by the slow coagulation of recalcified oxalated plasma previously freed of its own platelets, is by itself very poor in thrombin. In fact, the mixture becomes, within twenty or thirty seconds, capable of coagulating almost instantaneously a suitable amount of oxalated plasma; in other words, the reaction of serum with platelets generates plenty of thrombin. It must be pointed out that this experiment closely resembles that of Morawitz except that platelets, instead of tissue cells, are added to the serum. Tissue cells and platelets both contain, we shall insist further on this point, one of the generators of thrombin, which may be called cytozym; the second one, the serozym, exists in the serum. It can be easily demonstrated that the reaction between serum and platelets, that is to say between serozym and cytozym, takes place only in the presence of soluble calcium salts, no thrombin appearing if the serum has been decalcified before the introduction of the platelets. Moreover, I shall further insist on the fact that the two substances unite, that is, they really consummate each other: indeed experience shows that when a serum has been treated a

first time with platelets, and correlatively has already furnished thrombin, this serum is subsequently incapable of reacting with a new amount of platelets; its serozym having been exhausted by the first reaction. It follows that a serum produced by the coagulation of a plasma rich in platelets, and which of course contains much thrombin, is considerably less rich in serozym, hence, is considerably less capable of reacting with new platelets, than is a serum derived from a plasma deprived of most of its platelets. This is precisely what experience shows. It is, therefore, highly advisable always to employ as serozym, a serum obtained by the coagulation of oxalated plasma which has been carefully freed of its platelets before recalcification.

Serozym is a thermolabil substance, easily destroyed by heat; no thrombin is produced when platelets are added to serum that has been exposed to the temperature of about fifty-six degrees. On the contrary, cytozym, the active principle of platelets, may be heated up to one hundred degrees and even higher without losing its properties; cytozym is thermostable and, furthermore, can be easily extracted.

A thick emulsion of platelets treated by a large excess of absolute alcohol gives an extract from which there is obtained by evaporation a residue soluble in alcohol, ether, toluol, chloroform; but insoluble in aceton, thus exhibiting the characteristics of lipoids and specially of lecithin; and which acts as a very powerful cytozym.

As we were able to show eight years ago, traces of this lipoid behave exactly like platelets, generating thrombin when added to serum, hastening the coagulation of recalcified oxalated plasma or causing the coagulation of spontaneously non-coagulable bird's plasma. The same lipoid, possessing exactly the same properties, may be extracted from tissues, for example, from muscles.

Such information being gathered about cytozym, what is serozym? Serozym is certainly furnished by the plasma, not by the cells. Platelets contain cytozym, they give thrombin when mixed with serum, but they are never able to liberate thrombin when kept in physiological solution or in distilled water, even in the presence of calcium salts. They consequently

contain only one of the mother-substances, not both of them. The lability of serozym towards heat allows us to presume this substance is of an albuminous nature. Its fragility would be a very serious hindrance to its isolation, but for one really fortunate property: the serozym shows a strong tendency to adhere to mineral precipitates, such as barium sulphate, or calcium fluoride. This is the reason why, as I discovered many years ago with Gengou, those precipitates, added to oxalated plasma, wholly suppress in the latter the property of coagulating by subsequent recalcification; one of the mother-substances, the serozym which is absolutely requisite for the production of thrombin and consequently for coagulation, has been entirely removed. As I could ascertain more recently with Delange, tricalcic phosphate is especially powerful as an absorbent. When diluted in physiological solution this substance gives a rather gelatinous emulsion, a very slight quantity of which, added to blood flowing from the artery, prevents its coagulation. By centrifugalization and pipetting off, a clear plasma is obtained, which always keeps fluid, even when platelet emulsion, or tissue extract, or lipoidic cytozym is added. This is easily understood; both mother-substances, serozym and cytozym, are equally necessary to the production of thrombin; it is of no use to add one of them if the other is absent. But such a plasma, which we may for sake of brevity call "phosphate plasma" clots under the influence of ready thrombin or, which naturally is the same, when both mother-substances are added. It behaves as an excellent reagent for the detection of thrombin; its composition closely resembling that of the original plasma, it may be considered as being a fibrinogen dissolved in a normal medium.

But tricalcic phosphate is endowed with a property which renders it remarkably available fer technical purposes. As is well known, it is capable of dissolving in physiological solution under the influence of a current of carbonic gas. Consequently, phosphate which, having been added to plasma, has absorbed the serozym can, after having been thoroughly washed, liberate, thanks to its own dissolution, the active principle it had withdrawn. We succeeded thus, Delange and myself, in performing

the isolation of serozym, which, on the addition of cytozym extracted from platelets, gave plenty of thrombin, so that in the course of the whole experiment the determinism of coagulation is in reality subjected to an analysis followed by synthesis.

As mentioned above, our assumption that serozym and cytozym are the generators of thrombin involves the idea that those mother-substances really unite to form a compound, which is thrombin. This ought to be demonstrated also with regard to pure cytozym; I mean a cytozym in the condition of a lipoidal extracted matter. If the union truly occurs, we may anticipate that a given quantity of serozym which already has been mixed with a sufficient amount of cytozym, thrombin being thus engendered, will be correlatively exhausted; in other words, will be no more capable of giving fresh thrombin when a new amount of cytozym is added. Such is, indeed, the case. Serum yielded by coagulation of recalcified platelet—free oxalated plasma is divided in two parts, lipoidal cytozym being added to one of them, the other portion being kept as it is. In the tube containing both serum and cytozym, thrombin appears, the activity of which, very strong at the outset, decreases very fast so as to become the following day quite attenuated. On this following day, lipoidal cytozym, and several minutes afterwards, oxalated plasma are added to both tubes; then, the tube which has the preceding day received cytozym shows no clotting or only a very slow one, the tube to which cytozym has been just added for the first time, clots almost instantaneously.

There is no need to remark that such an experiment affords the possibility of ascertaining whether the same cytozym, endowed with the same binding properties as the pure lipoid, exists either in fresh or heated platelets, or in tissue juice such as ground muscle. Adequate experiments show that serum which has already reacted with any one of such materials does not generate any more thrombin when subsequently brought into contact with any one of them. For example, serum to which lipoidal cytozym has been added no longer reacts either with the same lipoid, or with platelets, or with muscle juice, and conversely.

Without entering into detail, I may add that the manner in

which the two substances unite, closely resembles the mode of union of toxins and antitoxins; namely, that the process is not governed by the law of strict and constant equivalents, but takes place in varying proportions, thus seeming to result, not from true chemical affinities, but from contact affinity or molecular adhesion. But another fact, more noteworthy for the knowledge of the underlying mechanism of coagulation is disclosed by the determination of the lapse of time required for the union of both substances.

Serozym being found in serum may be assumed to exist also in the oxalated plasma from which this serum has been derived. Now if cytozym and serum are mixed, thrombin appears very quickly; in fact, in some seconds. But, and this fact is truly remarkable, if cytozym is added, not to serum yielded by coagulation of recalcified oxalated plasma, but to an identical oxalated plasma recalcified just before, that is at a moment when this plasma is still perfectly fluid, the appearance of thrombin is greatly delayed. In other words, serozym reacts with cytozym, quickly when present in serum, slowly when present in plasma. We thus reach the conclusion that the serozym does not exist in the same condition in plasma as in serum; that in plasma it is not still capable of reacting at once with cytozym. We may express the fact by saying that plasma contains proserozym instead of active serozym, one of the first phenomena of the whole process of coagulation being precisely the conversion of proserozym, unfit until transformed to unite with cytozym, into serozym capable of this reaction.

The idea that in original plasma or in circulating blood, serozym does not exist as such, I mean does not exhibit affinities towards cytozym, satisfactorily explains why intravascular injections of the latter substance are, as we ascertained, quite harmless. But the blood of such injected animals shows, when shed within about half an hour of the injection, a strikingly increased tendency to rapid coagulation; this fact being probably, as we pointed out, available for therapeutic purposes in cases of hemorrhage.

Is it now possible to investigate under what influence the

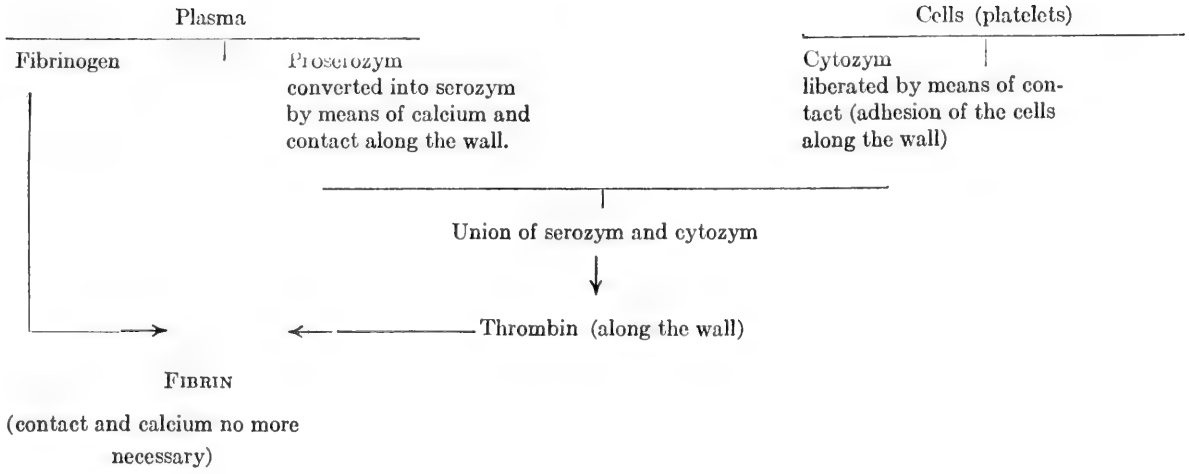
proserozym is converted into serozym, or in other words, acquires the capacity of reacting with cytozym?

To solve this problem, we have at our disposal a very adequate technic, based on the use of oxalated salt saturated plasma.

I recalled to your attention, some minutes ago, the fact that when oxalated plasma is saturated with common salt, the fibrinogen precipitates completely. After strong centrifugalization, pipetting off, and elimination of the excess of salt by dialysis in the presence of physiological oxalated solution, the supernatant fluid represents exactly normal oxalated plasma, except that having lost all its fibrinogen, it is no longer capable of coagulation. Being oxalated it does not contain any trace of thrombin, but is still capable of producing plenty of thrombin on addition of calcium salt and cytozym. Now if calcium salt and cytozym are added thrombin appears in fact, but only after a rather important delay. Half an hour, sometimes more, must elapse before the mixture becomes capable of causing an almost instantaneous coagulation of a fibrinogen solution. Then the ability to react with cytozym, that is, the conversion of proserozym into serozym, requires a notable length of time. Now on the other hand, the aforesaid fluid without fibrinogen being recalcified, cytozym is only added one or two hours later, then the thrombin appears almost instantaneously. This experiment clearly illustrates the essential assumption that the whole process of the production of thrombin, the first stage included, which is the conversion of proserozym into serozym henceforth capable of uniting to cytozym, takes its course without any participation of fibrinogen.

Furthermore, the conversion of proserozym, which as we know cannot take place without calcium salts, is, and the fact is noteworthy, strikingly favored by the contact of glass. The capacity of reacting with cytozym appears only after a much longer lapse of time when the recalcified fluid is maintained in a vessel coated with paraffin. Consequently, the influence of contact, which is so obvious in coagulation, is not exerted through some interference of fibrinogen, but really acts without any help of the latter, as a factor of thrombin production. It is highly probable that contact, by way of absorption, frees the liquid of some

SCHEME OF COAGULATION



antagonistic substance, most likely some protective colloid, which prevented the serozym from reacting with cytozym, that is, maintained it in the inactive condition of proserozym. On the other hand, experiment shows that the presence of cytozym likewise facilitates such a liberation of serozym, owing to its strong affinities towards the latter principle.

To sum up, we are now able to follow the scheme which indicates the order of succession of the phenomenon.

I think the scheme symbolizes quite accurately the most prominent features of the whole process and distinctly shows the sequence of events. But the mechanism underlying the coagulation as it occurs in the ordinary conditions is still somewhat more complicated, owing to a peculiar property of thrombin. Thrombin results from the union of serozym and cytozym, but these two substances combine in variable proportions. The consequence is that a given complex, when rich in serozym, is able to capture an additional amount of cytozym, and, when rich in cytozym, which is ordinarily the case in the coagulation of total blood, shows a marked affinity towards a new amount of serozym. As a matter of fact, such an affinity is so strong that it causes thrombin to attract and to possess itself of serozym even when this principle is still present in a state of proserozym. Consequently, ready thrombin acts as it could bring about a remarkably quick conversion of proserozym into serozym, the process preliminary to the genesis of fresh thrombin being thus greatly hastened. The consequence is that when thrombin is added to oxalated plasma which has been just recalcified, the total amount of thrombin this quantity of plasma is apt to furnish appears much more rapidly than it does when the same plasma is allowed to clot spontaneously without the impulse of thrombin. In fact, thrombin itself thus accelerates the formation of thrombin. Owing to lack of time, I cannot report here in detail the experiments which have established this idea, and I think I may now consider briefly some views held by certain authors which are rather out of agreement with the ideas developed above.

As is well known, my countryman, the physiologist Nolf, has adopted the rather unexpected theory of Wooldridge according

to which, instead of being the immediate determining factor of coagulation, thrombin on the contrary, is generated as a consequence of the coagulation itself. According to Nolf, the transformation of fibrinogen into fibrin is not the effect, but the necessary condition of the appearance of thrombin. Much of the data I recorded above energetically contradicts such a conception. For example, I have but to recall the experiments showing the production of thrombin in fluids altogether devoid of fibrinogen, and thus proving unquestionably that fibrinogen does not play any role in the production of the coagulating principle.

One important point has been and is still controverted; I mean the true significance of the lipoid to which we have so often alluded. Schmidt, who had already observed the accelerating influence, exerted by tissue alcoholic extracts on coagulation, believed that such lipoids made easier the production of thrombin, without assuming, as I do, that they really enter into its constitution. One of the most distinguished among the writers who have devoted their skill to the study of coagulation, Prof. Howell, especially directed his attention towards the fact that the lipoid extracted for example from nervous tissue is capable of inducing the coagulation of pepton plasma and hirudin plasma which, as is well known, keep fluid because they contain an anticoagulating substance called antithrombin. Contrary to our assumption, Howell thinks that the lipoid is not a constituent of thrombin, but acts because capable of neutralizing the antithrombin, which hindered the spontaneous conversion of prothrombin into thrombin. The real existence of antithrombin is, of course, unquestionable; and it is undoubtedly proven that antithrombin may be neutralized by thrombin, the two substances being, in all probability, capable of forming a compound. Now the question arises whether, when lipoid is added to pepton or hirudin plasma, the removal of the antithrombin function is due, as Howell claims, to the direct neutralization of antithrombin by this lipoid, or to a neutralization of antithrombin by thrombin generated under the influence of the same lipoid, the latter reacting with the serozym or proserozym also contained in the aforesaid plasma. In other words, according to this second interpretation, the

neutralization of antithrombin by the lipoid would be merely apparent or at least indirect, the direct agent of this neutralization being the thrombin the lipoid has caused to appear. I think such is in reality the conclusion forced upon us by recent and careful experiments of Gratia. Without the necessity of entering into the somewhat complicated details, those experiments have shown that the lipoid does not at all neutralize the antithrombin when the serozym or proserozym is previously removed, that is, when the production of thrombin is made impossible. Even when the lipoid is added in large excess, the abolition of the antithrombin function only occurs in proportion to the amount of serozym present, that is, in proportion merely to the quantity of thrombin that can be generated. Consequently, a direct influence of the lipoid on the antithrombin cannot be admitted.

Furthermore, Howell's view could hardly be brought into harmony with a very essential fact, mentioned above. Were his assumption correct, it should be admitted that serum yielded by the coagulation of recalcified oxalated plasma deprived of its platelets contains a large amount of antithrombin, since the addition of lipoid to such a serum, by itself poor in thrombin, produces in this fluid plenty of the latter principle. Upon the whole the serum should, in this respect, resemble very much the plasma from which it is derived. But, such being the case, it would be very difficult to understand why the lipoid neutralizes the antithrombin very quickly when added to serum, and very slowly when added to plasma. I think the only possible explanation of such a difference is that, in serum but not in plasma, as was said before, the serozym is capable of reacting very rapidly with cytozym to generate thrombin. However, the question as to the relation of cytozym with the antagonistic function is one of the most delicate in the whole study of coagulation: I fully realize that different views may still be upheld. As I told you when beginning, coagulation has been studied years and years by many investigators; none of them could presume that the problem is solved; every one of them merely induges in the hope of gathering some complementary data, a little more information.

URAEMIA*

DR. NELLIS B. FOSTER

Assistant Professor of Medicine, Cornell University Medical College.

IN his Harvey Lecture on Nephritis, Theodore Janeway stated three problems, the solution of which are necessary for a clearer conception of the symptoms of renal diseases. The problems were œdema, vascular hypertension and uræmia. At that time, 1913, we were studying uræmia in the belief that the solution of this question might aid materially in solving the others and possibly throw light on the essentially most significant problem, namely—the mode of production of nephritis generally.

By uræmia we understand an intoxication manifested my psycho-motor disorders, which is apt to supervene in nephritis. The term takes origin in the fact disclosed by the first chemical studies of body fluids of nephritics—the increase of urea in the blood and cerebro-spinal fluid, detected by Christison and Babbington. It was quite a natural inference that the retention in the body of considerable amounts of substances known to be waste products, since they were present in normal urine, should be considered responsible for the conspicuous symptom of epileptiform convulsions. The initial error in this deduction was the ancient enemy of medical science—faulty logic; and it required the energies of some of the best minds for the next half century to correct the conception. Owen Rees, it is true, objected to the current theory on the ground that larger amounts of urea were recovered from the blood of a case of obstructive anuria than had been noted in any case of Bright's disease; yet there had been in his case no nervous disturbances, no convulsive seizures. Subsequent results of animal experimentation cast a shadow of doubt on the theory which, however, was but slightly altered since

* Delivered November 20, 1920.

ammonium carbonate, the supposed precursor of urea, focussed attention (Frerichs) for a generation, until Oppler, under Hoppe-Seyler's direction, finally disproved the hypothesis.

The attention of students with a chemical bent turned to the extractives; but as theories based upon the idea of the toxic nature of uræmia weakened, the morbid anatomists advanced other theories based upon supposed changes in the central nervous system; e. g., inflammation of the arachnoid, œdema of the brain, general or local. Traube's attention was arrested by the frequency of serous effusions in nephritis; and this fact, together with cardiac hypertrophy and the increased arterial pressure, led him into a complex mechanical explanation of cerebral œdema.

The history of these early investigations is here merely outlined, because no abiding truth was revealed, no principle of wider application determined. This history is also an exception in medicine, since not here, as has so often happened, did the clinician separate out of chaotic disorder the several disease entities and state clearly the problem for solution. To a confusion of clinical entities must be ascribed the barren results of carefully done work. For example, the intimate relation between cardiac disorders and renal disease or their similarities, could not have been duly appreciated till a later date, nor the types of cerebral accident that might result.

Now, while the term uræmia may be inexact, yet it has won a general usage as descriptive of several symptom complexes accompanying nephritis. These symptoms fall roughly into groups; thus headache, vomiting, diarrhœa and amaurosis are styled toxic; then there are psychic symptoms; hallucinatory-parnoid states, stupor and coma, and motor symptoms;—transient paralyses, paresis and hemiplegia and convulsions. Careful clinical studies have shown that of these symptoms some are apt to occur together, while others are more or less fortuitous. And so there has grown up a conception of types of uræmia: (1) the convulsive or epileptiform type being the earliest one recognized in Bright's time; with this epileptiform uræmia headache and sudden amaurosis are often precursors and coma a sequel. The convulsive seizures and not infrequently recovery are the striking

features. (2) A second type never displays a sudden onset, but is marked by gradually deepening coma, unaccompanied by psychic disorder or signs of motor irritation. (3) A third type shows visual disturbances only when demonstrable lesions of the eye are present (hæmorrhages, exudate, neuritis, which is in contrast to the blindness of the first type of uræmia); and is prone to gastro-intestinal and psychic disorders, of which the latter are commonly hallucinations and paranoid delusions. Convulsions do not occur, lethargy and somnolence are the rule, and coma is terminal.

The association of symptoms into groups is not alone because they seem most commonly thus associated in disease, but also because each of these symptoms complexes appears often as a result of certain disturbances in renal function; and, furthermore, these uræmic types have each a more or less clearly defined disorder of metabolism. It will be my endeavor to present to you the evidence for these statements.

It has doubtless been a great handicap to study that pathology has not been able to discover in uræmia lesions of the central nervous system with sufficient constancy to correct clinical judgment. The diagnosis of uræmia can only be suspected from the character of organic change found post mortem. Aside from the lesions in the kidney and occasionally ulceration in the lower gastro-intestinal tract, uræmia leaves inconstant signs. Since the symptoms are so largely those related to the central nervous system, attention has been given chiefly to search for cellular alteration in the brain and cord.

It is well known that some increase of fluid in the ventricles and meninges post mortem is but an expression of the agonal transudation that occurs in all serous lined cavities, and is therefore of slight significance. This explains the œdema of the brain noted so constantly by early students, notably Rees. The question of cerebral œdema must be approached with due caution because the problem has never received adequate attention. Very nice considerations are involved in any attempt to explain an increase of fluid in a closed chamber such as the cranial cavity. Suffice it here to say that the larger problem is not comprehended

and in many instances where the increase of fluid is but moderate we can not be sure of cerebral œdema unless there be an accompanying disorder, such as hyperæmia, to explain it. Roughly, there is differentiated an active and a passive œdema; and, although the weight of Traube's name focussed attention on œdema of the brain as an explanation for uræmia, the part played by the general circulation in this œdema, and hence by myocardial disease, was not appreciated till the work of von Recklinghausen. We recognize now that œdema may be due to circulatory disorders and that in nephritis there is especially apt to supervene as a late complication an œdema resultant upon myocardial insufficiency. This fact, now appreciated, often confused clinicians of the last century.

Quite different in causation probably is the œdema associated with the lesion styled serous encephalitis. Not confined to the meninges, the œdema of the central nervous system in uræmia has more similarity to serous encephalitis than to purely passive œdema. But with our knowledge of serous transudation, agonal or post mortem, this observation can not be forced. The question of œdema generally is an unsolved problem and one that might profitably be attacked by physico-chemical methods.

In its highest severity œdema of the brain appears with constancy in but one type or uræmia; that type where stupor and coma, without convulsion, without psychic or motor disorder, is the prominent nervous symptom. The clinical picture, in so far as referable to the nervous system, and the neuro-pathology are then in similarity with that of chronic alcoholism. That this œdema of the brain may bear a causal relation to stupor or coma is suggested at least, by the transient clearing of the mental state following removal of cerebro-spinal fluid, which in this type of uræmia is usually under increased tension. Cerebral œdema seems in these cases only a part of the general anasarca which is the prominent clinical symptom.

Definite cerebral hyperemia we have observed in only one type of uræmia. Difficult to estimate and therefore uncertain in mild degrees, this hyperæmia is in some cases beyond doubt, and in several instances it has been accompanied by numerous pinpoint

hemorrhages scattered generally throughout the brain substance. There was also at times œdema, the nature of which is uncertain. In brief, these lesions are not to be differentiated from those seen in morphine poisoning. Now the interesting fact to us was that, while this picture was not seen with constancy, it was the significant lesion in some cases dead of convulsive uræmia and was not observed in other types. Oedema in slight degree might or might not be present, often quite absent, and then the neuropathology of epileptiform uræmia stood, in some measure at least, differentiated from that of other types or uræmia. A conservative deduction from these observations is that two types of lesions are notable in the central nervous system and in their extreme degrees these lesions appear to be associated with definite groups of symptoms. Only in so far do they suggest differences in causal factors.

Since its recognition as a sequel to nephritis uræmia has been regarded generally as an intoxication and efforts directed to determine the cause were largely made by chemical methods. Down to the time of Bouchard it was believed that urine is poisonous, or contains a poison. And since the epileptiform type of uræmia was so easily differentiated, little attempt was made to discover variations in the clinical complex or to hunt for more than one immediate cause, all alike being a result of renal disease. Today we recognize that disorder of the functions of the kidneys may take several forms and conceivably some variability in nervous symptomatology might be expected. It is generally accepted that nephritis may be characterized by imperfect nitrogen excretion, or in other cases by defect in salt and water excretion. And we observe cases where the former condition prevails without evidence of the latter, hence when the two occur together we recognize not a third type, but a mixed complex, at least from a physiological aspect.

The older ideas held some truth buried, nevertheless, in a maze of misconceptions. It has been known for ages that persistent anuria leads to death. Rees objected to Christison's theory of urea poisoning on the ground that anuria due to stone did not induce convulsions, although fatal. This observation has been

repeatedly confirmed. It matters not whether anuria be due to obstruction of ureters, renal arteries or veins, or removal of both kidneys, the symptoms resulting are alike; the most notable being progressive weakness and an increasing somnolence, nausea, headache, stupor, terminating in death. None of the classical symptoms of epileptiform uræmia are noted; amaurosis, palsies, and convulsions are absent. The renal arteries or veins, or ureters, were ligated in a number of dogs, which were observed carefully by us, but there was no clinical resemblance to a uræmic picture of the convulsive type. I studied with the greatest care from day to day three individuals who had been deprived of the only functioning kidney by emergency operations. In none of these were there the slightest evidence of irritability of the motor nervous system, nor impairment of the psychic functions until the last days of life. None had amaurosis, muscle spasms, paralysis, nor convulsions. All alike experienced first weakness, slight vertigo, mental dulness, then, a tendency to sleep which lapsed into coma, with death on the ninth to eleventh day after the operation. The blood in all of these cases showed a higher concentration of nitrogen and urea than usually occurs with uræmic patients. Similar symptoms were experienced by Hewlett and his two assistants following the ingestion of large amounts of urea. In one experiment enough urea was taken to raise the blood-urea up to 240 mg. per cent. All suffered from the same symptoms, differing only in degree; nausea, headache, vertigo, mental irritability, apathy and somnolence.

It is our conception that one type of uræmia is due chiefly to the retention in the body of substances normally excreted in the urine. The conditions leading to anuria induce symptoms resembling in certain respects (weakness, somnolence, etc.) asthenic uræmia, but there is not a complete reproduction of the complex. At first glance it would seem that these conditions of anuria are exactly and perfectly analogous to those of nephritis since they effect an extreme nitrogen retention. That this is not entirely true will appear on further examination of the problem.

A number of years ago Voit studied the toxicity of urea and

several other urine elements and found that he could feed dogs large amounts of urea in their food without apparent injurious result, provided the animals were permitted as much water as they desired. If, however, the water were limited to very small amounts, or withheld, symptoms such as vomiting, lethargy and ataxia developed. This observation contains a principle which is applicable to the conditions observed in chronic nephritis with nitrogen retention. This principle I must explain. We have been able to show in our studies of cases of chronic nephritis with nitrogen retention that the amount of nitrogen excreted in the urine bears a relation to the volume of urine. This fact was determined in this way: Cases with no defect in water execretion were given diets containing a definite known amount of nitrogen, the only variable being water; and it was then observed that if we gave much water no nitrogen was retained in the body, all being excreted; but if water were limited to less than a liter per day, nitrogen was retained and after a period the blood analysis showed an increasing amount of urea and non-protein nitrogen, in other words, an accumulation of nitrogenous waste. This is experimental confirmation of a well established clinical doctrine, namely, that these cases of chronic nephritis with nitrogen retention require much water in order to eliminate the nitrogenous waste, because the diseased kidney can execrete only at a low level of concentration of urea. Senator warned of the danger of uræmic symptoms if water be withheld.

It now becomes evident that the comparison of the metabolism of a patient with anuria on the one hand and one with nephritis and nitrogen retention on the other hand reveals an important difference. Both alike lose a definite amount of water through the lungs, but the patient with anuria loses no water through the kidney, consequently, even though nitrogenous substances are retained, water also is retained and the concentration of nitrogen in the *tissues* is thus relieved for some time. Furthermore, in nephritis the kidney excretes selectively, some substances with relative ease, others with increasing difficulty, so there results in disease selective concentration. All the nitrogen components of urine are not retained in equal degree, but some more than

others. This fact defines a contrast in the kind of nitrogen retention of nephritis to that of anuria. With anuria all the substances normally excreted in the urine are held back in the body; with nephritis, on the contrary, some are retained more than others. Now does the examination of blood in these two conditions accord with theory? In nephrectomized dogs we noted that urea formed 60 per cent. or over of the non-protein nitrogen. In the anuria of mercury poisoning the urea ran as high as 90. per cent of the non-protein nitrogen in some cases and was generally high. With uræmia, however, while both urea and non-protein nitrogen may be high, the urea nitrogen forms a smaller percentage of the total than with anuria—seldom over 65 per cent. and often below 50 per cent. of the total. We find then just the difference we should expect theoretically. In chronic interstitial nephritis this process of heaping up nitrogen waste is gradual and the cells become tolerant to abnormal amounts of these urinary elements. An excellent example of the effects of retention in the body of nitrogenous waste products consequent to desiccation is observed in cholera; a uræmic syndrome is one of the late complications of cholera, although the accompanying nephritis is not of severe degree. Here the extreme loss of water from the body in the stools results in actual desiccation; the specific gravity of the blood may rise to 1060. Accompanying this there is also an increase of nitrogen waste due to an increased katabolism of protein consequent to the infection. A similar condition of affairs I have observed in diphtheria; anuria due to desiccation leading to asthenic uræmia and at autopsy no significant lesion being demonstrable in the kidneys. The dryness of the tissues in these cases is well known.

But the best illustration of the relation which water excretion bears to the onset of uræmic symptoms in nephritis with nitrogen retention is offered by the effects of diuresis. Addison remarked that uræmia resulted when certain cases of Bright's disease with œdema developed diuresis and the œdema subsided. This is now a common observation; and uræmia may be not only a consequence of water loss through the kidneys but may also follow diaphoresis or restriction of the fluid ingested. All of these

conditions, diuresis, diaphoresis, or restricted fluid ingesta, result in a concentration of waste products in blood and tissues in cases of nephritis. There is then not the perfect analogy between anuria and the nitrogen retention of nephritis which has been supposed.

The chemistry of the blood has been well studied in asthenic uræmia because this is the most common type. It is now well known that all of the nitrogenous bodies found in urine are generally increased in the blood; some bodies more than others. In addition, we have observed that the amounts of nitrogen retained in the body by very sick patients (the difference between the nitrogen ingested in food and that excreted in the urine, feces, etc.) could not be accounted for by the non-protein nitrogen of the total blood in the body. These two facts led us to analysis of tissues post mortem. In brief, it has been quite definitely learned, I think, that the tissues retain more of these katabolic products than does the blood. In fact, there is some ground for the opinion that the excess in blood expresses a super-saturation of tissues; but this is not demonstrated.

In the range of problems yet unsolved is the question of the physical state of these organic compounds in the body fluids. Are they merely in solution or are they in combination with colloids? Although yet not determined, the latter state seems, however, more probable, and these colloidal compounds would then be directly influenced by various conditions, such as H-ion concentration. It will be recalled that the acidosis theory of uræmia has repeatedly been advanced at first by Senator, and while acidosis is often detectable it is usually significent in degree only in the terminal period of life. But exceptionally acidosis may be a prominent factor (V. C. Myers), and it is of interest that appropriate alkaline therapy then ameliorates or quite relieves the uræmic symptoms. This is an unusual manifestation.

We see then that asthenic uræmia is a complex syndrome, the chief components of which I have attempted only to indicate. The objection to the hypothesis of intoxication by excretory compounds loses force on careful scrutiny, since nephritis is comparable to anuria only in certain aspects: In one case, anuria, we observe the effects of a sudden overwhelming dosage; in the other

case, asthenic uræmia, we observe the results of slow cumulative poisoning from the same elements but in different proportions. There is as much correspondence of symptoms in the two conditions as we should expect, more similarity, in fact, than exists between the clinical effects of large toxic doses of known poisons and the slow cumulative effects of that poison. There is also found the difference in chemical composition of body fluids which we should theoretically expect to find.

For a generation after Bright the term uræmia was applied chiefly to a symptom complex characterized by epileptiform convulsions. The extension of the definition to cover the various types of intoxications which we have been discussing was of later development. The striking features of the epileptiform type of uræmia in some respects seems to differentiate a separate and peculiar entity. Without premonitory symptoms in many cases there occur sudden and violent convulsive seizures, transient palsies and hemiplegia and a peculiar form of blindness unassociated with detectable cause in retina or nerve; a recovery and return to health in some instances, as Addison observed—these symptoms are in such sharp contrast to asthenic uræmia that they suggested the effects of a peculiar toxin. The disorder has always been regarded as an intoxication. The explosive character of the symptoms aided correct diagnosis and study, in contrast to the insidious onset of other types of uræmia easily confused with various cerebral accidents.

From time to time attempts have been made to demonstrate the presence of a toxic substance in the blood from cases of convulsive uræmia, but none met with convincing results; nor has it been shown that urine from these patients is either less toxic or more toxic than normal. Each one of the organic substances excreted in urine was tested for its toxic properties a generation ago, but with no result, unless one consider the experiment of Landois, who applied creatinine to the brain cortex and elicited convulsive seizures.

If convulsive uræmia be an intoxication, as the older students conjectured, then the toxin is probably recoverable from the blood or tissues.

When urine is subjected to fractional analysis we find that

the various bodies composing the non-colloidal nitrogen are known down to a small per cent. Thus 75 to 85 per cent. is urea, the remainder ammonia, uric acid, creatinine, etc., and an insignificant fraction only is in doubt. Now, turning to blood, the non-protein nitrogen or filtrate nitrogen is composed of known elements only in part. The sum of the known bodies totals, at most, only about 80 per cent. of the total filtrate nitrogen, and this sum may fall to less than 50 per cent. of the total non-protein nitrogen of blood. Much less is known concerning the crystalloids of blood than of urine. Since we observed that the unknown fraction was large, not only in nephritis, but in the blood of healthy individuals generally, our first suspicion was that amino-acids made up a considerable part of this unknown nitrogen. But this idea proved to be incorrect. The amino-acid fraction varies but little and is not appreciably increased in nephritis with nitrogen retention. This fact, nevertheless, had considerable interest to us, because since this undetermined nitrogen is not composed of amino-acids, then it is probably not destined for cellular nutrition, but, on the contrary, is a katabolic product, a precursor of some known urinary element. The definite fact gained from our studies in fractional blood analysis was that a large fraction of the non-colloidal nitrogen of blood consists of substances not found in the urine. This fact opened certain possibilities for study which had seemed useless so long as the search for a uræmic toxin was restricted to the well-known ingredients of urine. From this time our energies were directed toward the isolation of various organic substances from the blood of patients suffering from convulsive uræmia and testing these substances on animals. This is not the time to discuss intricate chemical methods employed for fractioning the blood, since they have been reported elsewhere. Suffice it to say that in analysis of blood two difficulties must be surmounted: First, to separate all protein without affecting any chemical change in the protein molecule that might produce cleavage products, and for this only colloidal methods are suitable and the second difficulty to be met is the ever-present possibility of altering some non-toxic substance into a toxic one through chemical reagents. It is also to be remembered

that chemical reagents might likewise transform a toxic body into one relatively harmless.

By employing colloidal methods all protein can be separated from blood and a water clear filtrate secured which gives no reaction for protein by any test. In general, the methods employed in our work were, with slight changes, those commonly used by Bio-chemists for the separation of alkaloidal bases. An alcoholic solution of the hydrochloride is finally secured from which a crystalline salt separates on the addition of gold or platinum chloride. These crystals may be purified by recrystallization, broken up with hydrogen sulphide and the pure base recovered for tests on animals.

Considering the relative body weight of man and guinea-pig there should be sufficient toxin in 200 c.c. of blood from an uræmic patient to produce definite symptoms in the guinea pig. This we employed as our standard. The amount of toxin in 200 c.c. of blood is a fraction of a milligram. The base was dissolved in one cubic centimetre of normal salt solution and injected into the peritoneal cavity. This in outline was our method. We had now examined samples of blood from twenty-two cases of epileptiform uræmia and from over twice as many controls. For controls we used blood from other types of uræmia and cases of anuria, epilepsy and also normal individuals. From none of these control samples has a toxic substance been isolated. When, however, the solution of the base from the blood of cases of epileptiform uræmia was injected into a guinea pig the result has been uniformly fatal. The first symptoms usually appear about five minutes following the injection. There was rapid breathing and muscular twitching; this often followed by a series of convulsive seizures, terminating in death in a few minutes. In other cases the animals showed paresis of the hind legs, and had frequent bowel movements before convulsions develop. A few did not have definite convulsions, but severe twitching movements accompanying a stuporous state terminating in death. The result of our investigations seemed to indicate that the blood of patients with epileptiform uræmic contains an organic base which is toxic. Usually not more than a few hun-

dred cubic centimetres of blood can be taken from uræmic patients, and from his blood but a very small amount of the base can be recovered, the most recovered was weighed in milligrams.

The question then arose, had we perhaps made this organic poison by our chemical procedures? The possibility remained that the blood of uræmic patients may contain some substance not present in blood normally, nor in other diseases, and that our chemical manipulation so altered the nature of this substance that it became toxic. To determine this possibility we dialized blood from cases of convulsive uræmia against distilled water, then this diffusate was reduced to a small volume at low temperature and tested on animals. These diffusates are of course a mixture of all the non-colloids of blood. The interesting fact is that those samples from uræmic patients were usually quite toxic, while other samples were inert.

The substance isolated is basic in its properties and forms crystalline salts with platinum and gold. Of its chemical nature we know next to nothing because we have never been able to collect a sufficient quantity for analysis. Probably our chemical methods are quite imperfect and we either lose or destroy much in preparation. And in criticism of the work it is necessary to state that the existence of a toxin in uræmic blood will not have been demonstrated until its chemical identity is known. That is the only assurance against the effect of reagents upon unknown and possibly labile organic compounds. Apparently we are dealing with a substance as poisonous as strychnine, the amount of which in the body at any one time being possibly but a small fraction of a gram. We can easily conjecture several sources of such a poison in the precursors of known organic extractives. Especially inviting is the idea of reversible reactions in this connection, whereby the accumulaton in the body fluids of a katabolic product results in the increase also of its immediate precursor, which is often toxic but normally present in only the minutest amounts.

Uræmia presents a complex and intricate problem; and I do not wish to leave the impression that we now understand the clinical manifestations and their immediate causation. My thesis has been to indicate some of the more important

components in uræmic states and the probable origin of these individual factors. As in nephritis we conceive of specific renal functions and that the disorder of each alone or in combinations produces various symptoms, so in uræmia our conception is of several simple types, each a resultant upon a peculiar metabolic defect. These simple components or types, frequently merging in various combinations, effect the varied syndromes we name uræmia.

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THE PRESENT STATUS OF CARDIODYNAMIC STUDIES ON NORMAL AND PATHOLOGICAL HEARTS*

DR. CARL J. WIGGERS

Professor of Physiology, Western Reserve University

THE experimental or clinical investigator who essays to study circulatory problems that directly concern vital phases of medicine is frequently handicapped because certain fundamental data, which are the key to the interpretation of these problems, are not included in our stock of general information. It is desirable, therefore, first to review briefly some recent experiments which, I believe, help to clarify our understanding of the normal contraction processes in the heart. This accomplished, the laws which govern cardiac behavior will be analyzed. Finally, an effort will be made to see how far these laws may be applied in the interpretation of pathologic conditions with which we are confronted in the clinic.

I. THE FUNDAMENTAL MECHANISMS OF THE HEART RATE

The Physiology of Auricular Systolé.—The cardiac cycle is generally described as consisting of auricular systole, followed promptly by ventricular systole and diastole. It has long been known that certain quantitative differences exist between the contraction of the auricular and ventricular musculature. Thus, the greater capacity of the ventricles for performing work and their longer contraction period are generally emphasized, even in elementary physiology. Recently, evidence has been adduced which indicates that qualitative differences also exist. The ventricles receive their impulses through the His-Tawara system in such an ordered manner that all parts of the ventricular myo-

* Delivered December 11, 1920.

cardium are virtually excited at the same time (Garten[1]; Lewis and Rothschild[2]). Consequently, we may assume that the entire bulk of the ventricular musculature begins and ends its contraction at practically the same moment.

It is different in the case of the auricular contraction. A few years ago, Lewis and his associates demonstrated that the impulses developed rhythmically in the sinus node, spread eccentrically over the arterial muscular tissues, exciting in succession each fractionate portion of auricular tissue. In this way, the more distal portions receive their excitation later than those portions more proximal to the cardiac pacemaker.

In 1916, I presented experiments[3] which led to the conclusion that, a short interval after receiving an excitation, each unit of auricular tissue undergoes a brief fractionate contraction lasting about 0.05 second and then relaxes—an interpretation that has recently been confirmed by Lewis and his co-workers.[4] Auricular systole begins with the first fractionate contractions near the sinus node, and ends when a balance of the fractionate relaxations and contractions causes no further decrease in the length of the entire auricle. Since the fractionate units excited first begin to relax during mid-systole, the pressure in the auricles and large veins rises only during the early half and decreases during the latter half of auricular systole. We may therefore divide auricular systole into (a) a dynamic phase, during which blood is injected into the ventricles and (b) an inflow phase, during which some blood actually flows into the auricles from the central veins.

The Consecutive Phases of the Ventricular Cycle.—In order to interpret the dynamic mechanisms of the ventricles, it is sometimes desirable to subdivide their periods of systole and diastole into shorter phases. In doing this, synchronous pressure curves recorded by optical manometers from the cardiac chambers

[1] Garten: Skand. Arch. Physiol. 29: 114, 1913; Ztschr. f. Biol. 66: 23, 83, 1915.

[2] Lewis and Rothschild: Phil. Tr. Roy. Soc. London 206: 181, 1915.

[3] Wiggers: Am. J. Physiol. 42: 133, 1916; 40: 218, 1916.

[4] Lewis, Feil and Stroud: Heart 7: 131, 1920.

and aorta, together with ventricular volume curves, are of great assistance.

While it would be tedious to describe, even superficially, the apparatus and technic required for recording pressure and volume changes accurately, the principles of such apparatus can be outlined in a few words.

Suppose (Fig. 1) that small chambers, A, B and C, filled with fluid and covered by very tensely drawn rubber membranes, are inserted through the auricular and ventricular walls and into the aorta. Each membrane will then respond to every pressure variation by a microscopic movement. This can be magnified and rendered visible by reflecting a narrow band of light from a small mirror fastened to the rubber. By allowing these beams to focus on a film (D) moving in a specially constructed camera, a true picture of the pressure variations can be recorded.

In order to record the volume changes of the ventricles, they are slipped as far as their a-v junctions into a glass oncometer covered by a rubber diaphragm in which an opening, corresponding in shape and size to the a-v ring, has been cut. This oncometre is connected with a large recording tambour. When blood is expelled and the ventricular volume decreases, the volume of air in the tambour is reduced by a corresponding amount, and the tambour lever falls. When the volume of the ventricles, on the other hand, increases as blood flows in during diastole, the lever rises. By connecting the interior of the large tambour with an optical segment capsule, the very slight pressure variations which correspond to the volume changes may be projected and recorded optically (Henderson[5]; Wiggers[6]).

While the conformation of such volume and pressure curves alters under different experimental conditions and varies also in different animals examined, their general character and the time relations are represented fairly well by the curves shown in Figure 2. A careful study of many kilometers of such records obtained from over 200 dogs under a large variety of experi-

[5] Henderson and Collaborators: Am. J. Physiol. 16: 325, 1906; 23: 345, 1909.

[6] Wiggers: Circulation in Health and Disease, 1915, Phil., Lea and Febiger.

mental conditions, together with a careful consideration of similar dynamic studies carried out by Garten,[1] Piper, Straub[7] and C. Tigerstedt, have led me to interpret and subdivide the ventricular cycle as follows: At the onset of ventricular systole (Fig. 2, I) the pressures within the auricle and ventricle are approximately equal. At this time, as indicated by the experiments of

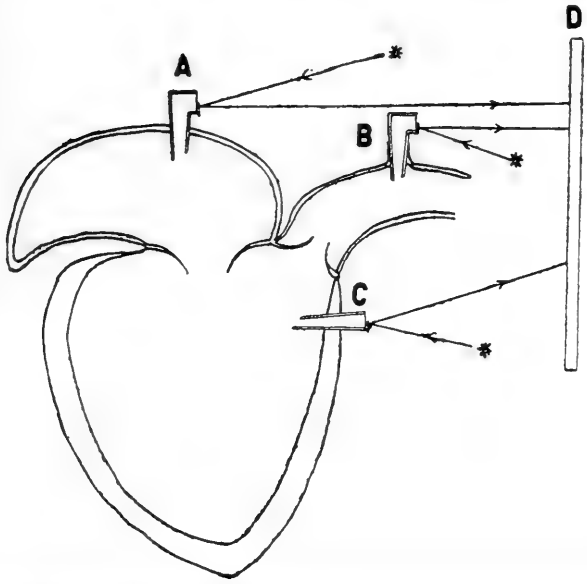

FIG. I.—Schematic representation of principles employed to record pressure curves optically from auricles (A), ventricles (C) and aorta (B). D, sensitive photographic surface. Description in text.

Dean,[8] the a-v valves are in the act of floating into apposition. As Henderson and Johnson[9] suggest, this movement probably of the pressure rise (I) until the opening of the semilunar valves is initiated by the sudden cessation of the jet when the peak of the presystolic auricular wave is reached. The first elevation of intraventricular pressure firmly closes these valves, and the ventricles then contract in an absolutely isometric fashion. This first phase of ventricular systole, extending from the beginning

[7] Straub: Deutsch. Arch. f. klin. Med. 115: 531, 1914; 116: 409, 1914.

[8] Dean: Am. J. Physiol. 40: 206, 1916.

[9] Henderson and Johnson: Heart 4: 69, 1912.

of the pressure rise (I) until the opening of the semilunar valves (II), is preferably designated as the isometric contraction phase.

As soon as intraventricular pressure exceeds intra-aortic pressure, the semilunar valves open and a comparatively large vol-

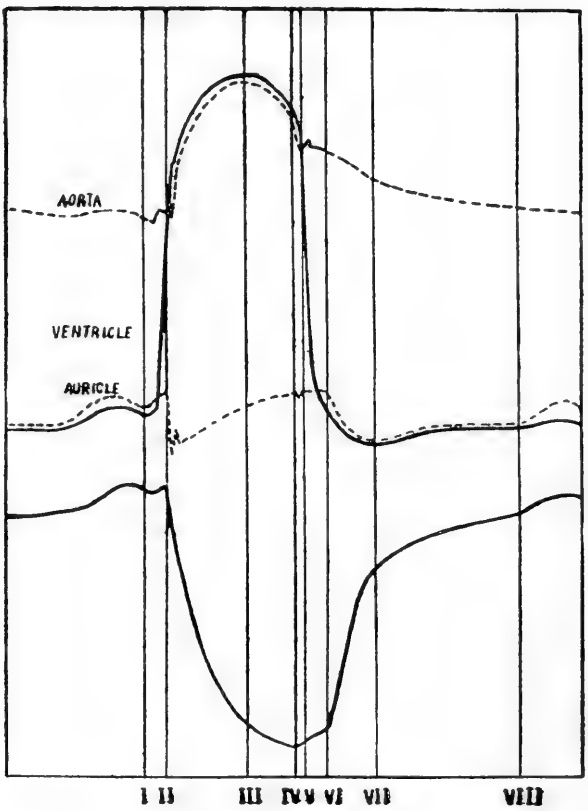

FIG. II.—Superimposed curves of pressure changes in ventricle (heavy line), aorta (upper dotted line), and auricle (lower dotted line) together with volume changes in two ventricles (lower solid line)- I-IV, systole; IV-VIII, diastole. Detailed phases of each discussed in text.

ume of blood per unit time is ejected. As long as the volume ejected remains greater than the outflow from the peripheral arterioles the aortic and intraventricular pressures continue to rise. This summit (III) marks the end of a second phase of systole which I have designated as the maximum ejection phase. As soon, however, as the volume of the systolic discharge decreases

to such an extent that it no longer equals the peripheral outflow, the aortic and intraventricular pressures begin to decline. This third phase (extending to IV) may be designated as a phase of reduced ejection. It terminates the period of systole.

At the onset of ventricular relaxation, aorta and ventricle are still in communication. The first event, viz., the approximation of the semilunar valves, is signaled by a sharp drop in both aortic and intraventricular pressures (IV-V), designated as the incisura. This marks a fourth or protodiastolic phase of the ventricular cycle. Following the closure of the semilunar valves (interpreted as taking place at V) and until the a-v valves have opened, the ventricle relaxes without any flow of blood either from or into its cavity. This phase (extending from V to VI) may be designated as the isometric relaxation phase. With the opening of the a-v valves (VI), a rapid ventricular inflow begins. This continues until an equalization of pressure between the auricle and ventricle has taken place (VII), or until a subsequent systole interrupts the filling. This is the sixth phase, which may be designated as the early diastolic inflow phase. In long cycles, and when auricular pressure is normal, a period of reduced filling or approximate stasis is indicated in the volume curve (VII and after), which may be designated, after Henderson's suggestion, as the phase of diastasis. Finally, there may be added an eighth phase during which the dynamic interval of auricular systole (VIII) affects the filling or pressure of the ventricles. This summary of the dynamic events occurring during ventricular systole and diastole and the suggested subdivision of the periods of systole and diastole into shorter phases is schematically indicated in Figure 3. On the diagrams are also indicated the average duration of these consecutive phases recently found in animals in which the thorax remained intact.

II. THE LAWS GOVERNING CARDIAC BEHAVIOR UNDER NORMAL AND ABNORMAL CONDITIONS

Under a variety of physiologic, pharmacodynamic and pathologic conditions, the heart must adapt itself to an altered venous return and changes in arterial resistance. In association with or quite independent of these, changes in rate and rhythm may

take place. Again, the inherent functions of cardiac irritability and contractability may be stimulated or depressed.

When such a combination of influences unites to modify the cardiac mechanisms, it may become quite perplexing, if not hopeless, to analyze the factors responsible for the resulting cardiac behavior. It is quite probable that this accounts for the observa-

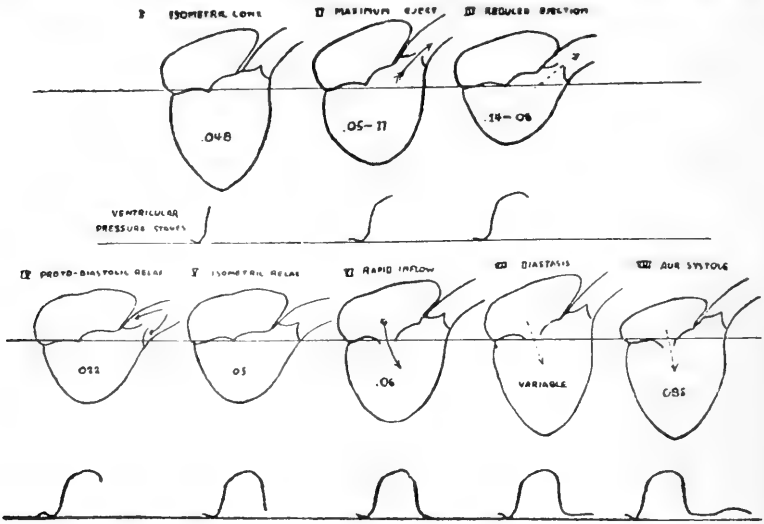

FIG. III.—Series of pictorials illustrating the consecutive phases of the cardiac cycle established from pressure and volume curves. The extent of the ventricular pressure variations that have been completed at the end of each phase are also indicated. Upper series, phases of systole; lower series, phases of diastole.

tions (1) that "clinical hearts" do not always seem to conform to the laws and reactions established by laboratory experiments, and (2) that they do not always react to drugs as do the hearts of experimental animals.

It is important, therefore, that the laboratory investigations concern themselves primarily with the alteration produced in cardiac behavior when, as nearly as possible, only one of these variable influences operates at a time. The history of such researches has been the history of all investigations involving the use of complicated apparatus to unravel the mysteries of complex functions. One investigator demonstrates a series of striking

facts; their uniformity suggests that they are grounded on a common factor or principle; a theory or law of cardiac behavior is formulated. Another investigator discovers certain facts which it is difficult or quite impossible to harmonize with such a conception. The older law is apt to be considered disproven and a new one is formulated. Rebuttal and countercharges supported by new and still newer experimental facts fill many pages of scientific literature until he who follows every development cannot always decide what to believe either in his own work or in the experiments of others.

With the many differences of opinion regarding the fundamental laws controlling the functions of the heart beat, it is possible to keep from falling into this hopeless mental state only by bearing in mind that the disapproval of certain interpretations does not necessitate the discard of all experimental facts arrayed in its support. On the other hand, an investigator may have established a broad principle and yet have failed to realize the limitation of its applicability. We must admit, I believe, that while each new series of experiments has contributed its building stone, there still remains to be hewn out of unknown facts the keystone to that group of laws which regulates the heart beat under diverse conditions of circulation.

The Heart Rate as a Factor in Controlling Cardiac Efficiency and the Law of Uniformity of Behavior.—In a large series of experiments, Henderson and his co-workers[5] have contributed greatly to our understanding of the cardiac mechanism. They have demonstrated by experiments, that to me seem not to be negatived by apparently contradictory results of other investigators, that the ventricular filling occurs chiefly during the earlier portion of diastole, and that, in slowly beating hearts, there exists a phase of diastasis during which a very gradual filling of the ventricle takes place. They have done much toward demonstrating that the blood volume received by the ventricle during diastole also determines the amount discharged during systole. They have analyzed how variations in ventricular tonus can modify both filling and systolic discharge. They have demonstrated how, as the heart accelerates and the cycle shortens, the succeed-

ing diastolic filling is encroached on more and more until the diastolic inflow is abbreviated and systolic discharge is greatly affected. That this tendency of the systolic filling to be decreased as the heart accelerates is one of the fundamental compensatory mechanisms which prevents an excessive minute volume from being discharged during rapid heart action, cannot be questioned. Henderson and his collaborators maintain further, however, that both under normal conditions of venous return as well as during states of increased venous pressure, the systolic discharge cannot be further affected by the venous pressure change or volume of venous return, but hold that it is determined solely by the duration of the cardiac diastole. They found that the volume curves of the ventricle, at any heart rate, are practically superimposable on portions of a standard curve obtained during a slow beat. This led them to formulate the "law of uniformity of cardiac behavior," according to which the systolic volume discharged is entirely a function of heart rate as long as the venous pressure is at or above normal.

The strict operation of this law has been questioned by subsequent investigators because it does not appear to square with other experimental evidence. In 1914, I[10] found that systolic and diastolic blood pressures in man vary, independently of heart rate, which was interpreted to indicate that the rate of ventricular filling in man must alter during normal inspiration and expiration. Henderson and Haggard[11] have subsequently attempted to nullify these experiments by showing that systolic and diastolic pressures, measured by the sphygmomanometer method in man, failed to increase when a person is tilted on a board from a horizontal to a head-down position—a procedure obviously increasing the venous return and auricular pressure. Such experiments cannot be regarded as crucial, however, for, even if it be admitted that the ordinary methods of estimating human blood pressure are sufficiently delicate to detect small variations, the fact that their experiments were always attended by heart rate changes,

[10] Wiggers: J. Exper. M., 19:1, 1914.

[11] Henderson and Haggard: J. Pharmacol. and Exper. Therap. 11: 189, 1918.

make it quite impossible to lend much significance to the pulse pressure change that occurred. On the basis of subsequent work, I am quite ready to admit, however, that my interpretation of pulse pressure changes during inspiration and expiration are more probably explained by a direct effect of the changing negative pressure on the aorta itself.

The view that the systolic discharge is unable to vary independently of heart rate when venous pressure is increased has been disputed by the results of Krogh,[12] Plesch[13] and Zuntz;[14] for it is difficult to explain the greatly augmented blood flow through the lungs during exercise in any other way than by assuming that the systolic discharge increases above normal even when the heart is very rapid. Krogh endeavored to show, furthermore, that such results may be harmonized with Henderson's volume curves if one or two assumptions is made, namely, either that the venous supply is normally inadequate, or that some myocardial factor increases the vigor of systole. Henderson and Barringer[15] again investigated the question as to whether the accelerator nerves can effect the amplitude of systolic discharge independent of rate—with negative results. Subsequently, Starling and his collaborators[16] re-investigated the subject by means of their "heart-lung preparation" and concluded that the ventricular volume curves are not superimposable. Their volume curves indicated to them that when venous pressure increases above normal, the systolic stroke is greatly increased without any change in heart rate. Similar conclusions have also been reached by Straub[7] and Socin.[17]

We may inquire what changes must necessarily take place if the systolic discharge increases at the same time that the heart accelerates. Obviously, such a condition is made possible only

[12] Krogh: Skand. Arch. Physiol. 27:126, 1912.

[13] Plesch: Centralbl. f. Physiol. 26:90, 1912.

[14] Zuntz: Ztschr. f. klin. med. 74:347, 1912.

[15] Henderson and Barringer: Am. J. Physiol. 31:228, 352, 1913.

[16] Starling and Collaborators: J. Physiol. 44:206, 1912; 47:275, 286, 1913; 348, 357, 465, 1914.

[17] Socin: Arch. f. d. ges Physiol. 160:132, 1914.

by an increase in the expulsion rate or by lengthening of the ejection phase. Recent experiments in which I measured the duration of systole after saline infusion indicate that this causes a definite prolongation of the ejection phase, quite independent of diastole length.

On the basis of recent experimental work, Katz and I[18] have found it necessary to conclude also that, even under quite normal conditions, the systolic discharge of the heart may not be regulated by changes in the duration of cycle alone. Our evidence is based on the following considerations: Although emphasis has not been laid specifically on the fact by Henderson and his co-workers, it is evidently a corollary of the "uniformity of behavior law" that the duration of systole is fixedly related to cycle lengths under all conditions which normally produce a change in heart rate. As the cycle shortens from a very long to a very short cycle, the phase of systolic ejection must, at first, be very little affected but becomes progressively shorter. By determining the theoretical systole and cycle lengths and expressing this as a systole : cycle ratio, it was found possible to construct a curve of theoretical s/c ratios. To this curve, the actual s/c ratios at different heart rates should conform if the law of superimposability holds good. It was found, however, that, while the actual s/c ratios obtained during normal rates and during vagus beats coincided reasonably well, the ratios were very much below this curve when the heart rate increased during stimulation of the accelerator nerve.

In carrying this work still further, Katz and I, working independently and by different methods, have obtained other evidence which indicates that during vagus slowing the periods of systole and diastole are also not strictly related to the length of previous diastole. When, for example, the peripheral end of a vagus nerve is stimulated with a current producing moderate slowing, systole increases in length for several succeeding beats, becoming stationary only when a new equilibrium has been established. This occurs regardless of previous diastole lengths and often contrary to them. After reflex slowing induced by central vagus stimulation, the duration of systole in a few experi-

[18] Wiggers and Katz: Am. J. Physiol. 53:49, 1920.

ments was longer than in peripheral vagus stimulation, even though a much greater slowing was produced by previous peripheral stimulation. When partial asphyxia produces cardiac slowing, the periods of systole may remain unchanged or even become abbreviated.[19]

Such results indicate that while a constant relation between

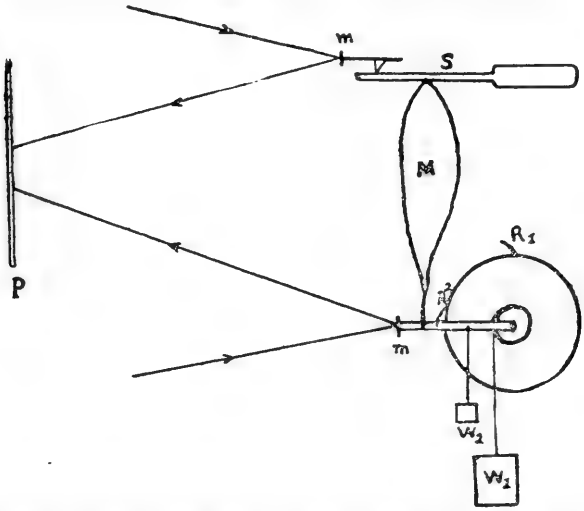

FIG. IV.—Diagram showing arrangement of muscle activating a work adder, with attachments for photographically recording tension changes and length changes optically. S, spring; m, small mirrors reflecting light beam to photographic film; P. Further description in text.

systole and diastole lengths, such as complete superimposability of beats demands, approximately obtains when a stable equilibrium has once been produced after direct vagus stimulation, there are other factors at work which more than counterbalance such a control of systole length.

On the basis of all these investigations, we must conclude that, while the systolic discharge is mechanically determined by the heart rate when other factors are unchanged, the simultaneous variations of these factors even under normal conditions prevent the beats from being superimposable.

The Response of the Heart to Changes in Venous Return and

[19] For subsequent extension of this work cf. Wiggers and Katz: Amer. Journ. Phys., 58, 439, 1922.

Arterial Resistance.—The response of the normal heart to changes in venous return and alterations in arterial resistance have been studied by recording both the volume curves of the two ventricles, and the pressure curves from the separate ventricles. While such methods have their difficulties and drawbacks, their use has served to advance our understanding of an important phase of cariodynamics. In order to grasp the significance of such investigations in their fullest, however, it is necessary to recall the nature of the contraction processes in a skeletal muscle which operates in a manner similar to the heart.

It has been pointed out by Henderson that, with certain reservations, the heart contracts as a skeletal muscle operating a work-adder. In such an arrangement (Fig. 4) the weight (W_1) which the muscle is required to lift is supported by the ratchet (R_1,) and, consequently, weights the muscle only during contraction. During the rest period, as well as during the process of relaxation, the muscle is stretched by a smaller weight W_2. Obviously, the greater this weight becomes, the greater the length of the resting muscle. This resting length of the muscle is referred to as its initial length. When this weight increases, the muscle fibers are not only lengthened more but are also placed under a greater tension, referred to as its initial tension. Changes in this initial tension may be recorded graphically and evaluated by attaching the upper end of the muscle to a stiff spring, the very slight movements of which can be greatly magnified and projected (Fig. 4). A muscle so arranged is said to be "after-loaded." Before it can shorten, its tension must be increased sufficiently to overcome the load W_1, i. e., it first contracts isometrically. Such a tension variation will be recorded by the upper lever a short interval before the lower lever begins to register a decrease in length. This accomplished, the ratchet R_2 engages and the weight is raised during the remainder of the contraction phase. Inasmuch as the tension during this phase of contraction does not alter appreciably, it is said to contract in an isotonic manner. At the onset of relaxation, the ratchet lever R_1 engages and the relaxation process is assisted by the small weight W_2.

In the normally beating heart, the venous pressure represents the distending load (W_2) and determines the initial tension as well as the initial length of the ventricular muscle fibers, while the arterial pressure corresponds to the lifted load (W_1). It is clear, therefore, that changes in initial tension as well as the tension changes during contraction and relaxation may be conveniently followed by recording optically the intraventricular pressures. Changes in the length of muscle fibres, as Frank, Patterson, Piper and Starling and others have pointed out, may be evaluated most satisfactorily by studying the changes in the ventricular volume during consecutive phases of the heart cycle.

In 1914, I reported[6] experiments which seemed to demonstrate that every increase or decrease in the volume of blood returning to the right auricle affects simultaneously the initial tension, height, and contour of the right intraventricular curve. These experiments were the first to demonstrate that the laws derived by Frank from a study of the frog's heart apply also to the naturally contracting mammalian ventricle. In brief, the conclusion seemed justified that *the gradient of the isometric pressure rise as well as the systolic pressure-maximum are determined by the initial tension* as long as marked changes in arterial resistance or alterations in the inherent contractility of the heart are not produced. At the same time, it was shown that any increase in pulmonary arterial resistance is also capable of altering the pressure-maximum in the right ventricle under conditions of unchanged venous inflow. Finally, it was pointed out that independent of, or coincident with these factors the pressure-maximum may be determined by the inherent contractility or irritability of the heart itself.

Shortly after the publication of this work, a series of investigations were published which apparently analyzed the reactions of the heart to increased venous return and increased arterial resistance in a much more fundamental manner. This was accomplished by limiting the circulation to the heart and lungs and controlling independently the venous inflow and the arterial resistance. With such a "heart-lung" preparation dynamic experiments were carried out in London, by Starling,[16] working

at various times in association with Knowlton, Markwalder, Patterson and Piper, and contemporaneously by Straub[7] in Munich. Subsequently Gessell[20] in this country, has utilized a similar method of experimentation.

The first investigations of Starling and his associates showed that the systolic discharge of the ventricle at any constant rate is unaltered by very considerable change in arterial resistance as long as the inflow is kept constant. On the other hand, they found that, within wide limits, the heart is able to increase its

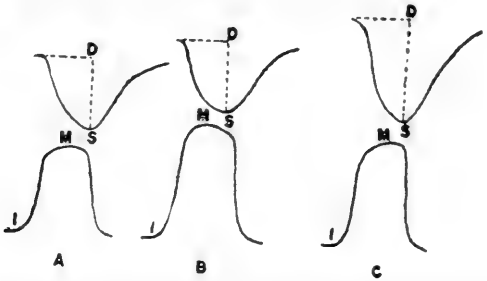

FIG. V.—Diagrammatic representation of ventricular volumes (upper curves) and pressure changes in left ventricle (lower curves), according to results of Patterson, Piper and Starling. D, diastolic volume; S, sytolic volume; D-S sytolic discharge; I, initial pressure; M, pressure-maximum. A, normal controls; B, after increased arterial resistance—initial pressure (I) unchanged, initial volume (D) increased, pressure-maximum (M) higher, sytolic discharge (D-S) unaltered. C, after increased venous inflow—initial pressure (I) decreased, initial diastolic volume (D) increased, sytolic discharge (D-S) and pressure-maximum (M) increased.

output in direct proportion to the venous inflow. Similar results were obtained by Socin[7] and de Heer.[21]

In studying the cardiac reactions more in detail, Patterson, Piper and Starling obtained results which are diagrammatically illustrated in Figure 5. Their records show that when the venous inflow increases, the ventricles are more distended in diastole and the systolic discharge increases (Fig. 5, A and C). The initial tension in the left ventricle, however, may not increase, but, on the contrary, may actually be lower. Nevertheless, the intraventricular pressure-maximum appears to rise.

When arterial resistance alone was raised, they again found an increased diastolic volume due to retention of blood during the first few beats. Their tracing indicates that once dilated to

[20] Gesell: Am. J. Physiol. 39:239, 1916; 40: 267, 1916.

[21] de Heer: Arch. f. d. ges Physiol. 148:45, 1912.

a stable capacity, the heart expels at least as large a systolic volume as before the increase in resistance (Fig. 5, A, B). In studying the intraventricular pressure changes accompanying such reactions, it was also found that the left intraventricular pressure-maximum increases, that the pressure gradient rises steeper and that the duration of the period of systole is increased. In some cases, however, the noteworthy observation was made that the initial tension is scarcely affected in the left ventricle. These results, together with observations on the isometric con-

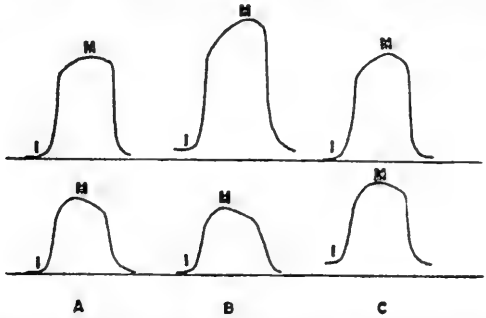

FIG. VI.—Diagrammatic representation of pressure changes in right (lower) and left (upper) ventricles according to Straub's results. A, normal control curves; B, after increased arterial resistance—initial pressure (I) increased in left ventricle, unaltered in right, pressure-maximum (M) higher in left ventricle, lower in the right. C, after increased venous inflow—initial pressure (I) increased in right but not in left ventricle, pressure-maximum (M) increased markedly in right and vero slightly in left ventricle.

traction curves obtained from the terrapin heart, led them to conclude that "in the reaction of the heart to increased venous inflow and increased resistance, the only factor which constantly varies with the response of the ventricles is the volume of the heart, i. e., the length of its muscle fibers." They believe, on the basis of such experiments, that we are justified in ascribing the increased energy of the cardiac contractions under conditions of increased inflow or augmented resistance entirely to alterations in the length of the muscle fibers and not to change in tension on the fibers, which, as they interpret it, may or may not be present at the same time.

The contemporaneous experiments of Straub[7] led on the whole to similar, yet in some vital respects, different conclusions. He also found that, under a constant venous inflow, increased arterial

resistance leads to a systolic retention both in systolic and diastolic distension. The systolic discharge remained unaffected. His optical pressure curves indicated, moreover, that, in the left ventricle, not only the maximum pressure, but also, the initial pressure increases (Fig. 6, of A and B). Such results, contrary to those reported by Starling and his co-workers, would indicate that an increased pressure-maximum is constantly associated with, if not fundamentally due to, an increased initial pressure. In the right ventricle, however, he found no increase in height nor elevation of the initial tension; in fact, in some cases, the pressure-maximum seemed to be reduced. These results, it will be recalled, are quite contrary to those previously reported by Fühner and Starling[16] who found that a "backing up" of blood always occurs when the left heart works against an increased resistance. In attempting to harmonize these discrepancies, Straub pointed out that he also was able to obtain such "back pressure" effects when the arterial pressure at the start was low and the coronary supply therefore insufficient to maintain the heart in prime condition. Straub considered the latter reaction as one of a hypodynamic and uncompensating heart; Fühner and Starling considered it the reaction of a normal heart. We shall revert to a discussion of this question later. When the inflow rate was increased but the arterial resistance kept constant, Straub found, similar to Starling and his co-workers, that the two ventricles dilate somewhat and expel larger systolic volumes. The intraventricular pressure curves taken from the two ventricles again showed differences (Fig. 6, A and C). In the right ventricle, changes similar to those reported by myself were constantly observed, i. e., increased diastolic filling always occasions an increased initial tension and a higher pressure-maximum. In the left ventricle and in confirmation of Starling's results, no changes in initial tension occur although the pressure curves did become somewhat higher. According to these results, the increased discharge of the right ventricle is unable to affect the diastolic filling of the left sufficiently to cause an elevation of initial tension. While Straub interprets his results as indicating that initial tension is the primary factor in determining ventri-

cular efficiency, the increased systolic discharge of the left ventricle must, in such cases, be assigned to changes in initial length or initial volume rather than initial tension.

In investigating the importance of auricular systole in the dynamics of the ventricle, Gesell,[19] was compelled to consider the broader question as to whether initial length or initial tension primarily determine ventricular efficiency. In the auricle of the river turtle, which shows rythmic fluctuations in tonus, he found it possible to study the effect of changes in tension and length independently. His results indicated that in the auricle of the turtle, increased strength of contraction may accompany either increased length of fiber while initial tension remains constant, or increased tension while initial length remains the same. Further experiments on a mammalian heart-lung preparation led him to conclude that this also applies to the mammalian ventricles. The latter experiments may not be regarded as quite conclusive, however, because the method employed to record variations in tension and length do not appear to be quite adequate for the study of the mammalian circulation. As a result of his work, Gesell suggests that, while both initial length and initial tension may determine ventricular efficiency, the surface-volume relations are also concerned.

With these conflicting views before us it seems desirable to re-investigate whether measurable differences of initial tension fail to accompany such experimental procedures as have been definitely shown to increase initial volume. This, I have recently attempted in intact animals. At once we may anticipate the loud objections that experiments carried out on intact animals can, of course, not prove valid either the one contention or the other.

Extensive experience has convinced me that it is not so difficult to control or evaluate the separate factors in intact circulation experiments as has been claimed. If the vagi nerves have previously been severed, variations in heart rate are no more extensive than those which occur in perfused hearts. The venous return may readily be reduced by compression of the vena cava and increased by the injection of innocuous normal saline. In neither event is arterial resistance altered appreciably. In-

creased resistance may be induced either peripherally by vasoconstriction or more centrally by mechanical compression of the aorta. If carried out for intervals which are short but quite long enough to obtain observations, the venous return is either not sufficiently affected or, if modified, can be evaluated in interpreting the reactions.

Are the experimental conditions in the heart-lung preparation better or more controllable? The very fact for which these experiments are lauded, viz., that each factor—venous inflow, arterial resistance and rate—may be controlled at will, makes them a source of trouble. In such schemes, it is the first duty of the experimenter so to adjust the artificial factors (the controllable factors) that the heart beats after a fashion which he interprets as normal. What criterion other than instinct can guide him? We have already pointed out that the adjustment of the artificial resistance to the inflow volume apparently determines whether or not a "back pressure" effect takes place on raising the arterial resistance. Each experimenter will be ready to admit that his adjustment approximates normal. Führer and Starling find "back pressure effects" as far back as the right auricle on increasing artificial resistance; Straub finds that the pressure in the right ventricle decreases. Both results cannot apply to the intact normal circulation. Who shall judge between them? I have been able to show in similar heart preparations that, with constant arterial resistance, an increased systolic discharge may cause either an increased or decreased pulse pressure in the arteries, depending on whether the arterial resistance during the so-called "normal" is relatively great or small, as compared with the venous inflow. Both reactions cannot be characteristic of the intact circulation. The fact that mean arterial pressure approximates the normal found in animals of course means nothing whatsoever. In short, I believe that in many instances it is possible to set the "normal" so that absolutely diverse propositions may be clearly (!) demonstrated with equal facility.

Aside from the judgment of the experimenter, we have possible alterations in the physiological condition of the perfused heart to deal with. Does it react as the heart in the intact cir-

culation? Always, it is separated from all nerve control—not without its effects on the duration and strength of ventricular contraction. Usually, also, the pericardium is opened—causing, as has been shown in Starling's own laboratory by Kuno, important changes in the distension of the ventricles. Commonly also, the capacity of the rubber tube substituted for the aorta is too small to accommodate, in a natural manner, the ejected blood, so that the entire systolic volume must each time be forced through a small cannula tied into the narrow lumen of the innominate artery. In the heart-lung preparation, the blood supply of the heart also changes in a manner which is quite abnormal, whenever the resistance increases. If the aortic resistance increases in the natural circulation, short circuits are always available through which an excess of blood may flow. In the heart-lung preparation the only short circuit is the coronary system which then apparently allows exorbitant volumes of fluid to flow through it. A few direct observations may be interesting: If we use the figures of Patterson, Piper and Starling, we can only conclude that normally from 25 to 35 per cent. of the entire systolic discharge passes through the coronary system, a volume which if correct represents a most abnormal state of the coronary circulation which certainly does not conform to the intact heart. Straub found that after compression of the aorta, the coronary blood flow increases so greatly that right auricular pressure is thereby augmented—a condition just the reverse of that obtaining in the intact circulation. Frequently also, the heart is supplied with a blood-saline mixture of unnatural composition. In Straub's experiments, for example, the deficiency of carbon dioxid in the blood, according to his own interpretation, caused the hearts to beat at the excessive rate of 300 per minute. Finally, it seems very doubtful whether the preparation accomplishes the task for which it is specifically employed. I question, for example, whether it is possible to alter any one factor—e.g.,—heart rate, venous pressure or arterial resistance—without at the same time affecting some other factor. Thus, it appears both from the records of Patterson, Piper and Starling and those of Straub that, whenever the arterial resistance increases consider-

ably, the filling pressure in the right auricle also augments. Again, I have found it exceedingly difficult in similar experiments to dissociate changes in temperature from changes in venous inflow; the two seem intimately interdependent. Whenever the inflow rate is increased, a tendency exists to increase the temperature of the heart muscle; when it is reduced, the reverse tendency exists. The temperature change may be only 0.5 C.; but what changes in inherent irritability and contractibility may not this induce! How can the influence of this factor be separated from that produced by augmented inflow itself? On the whole, who dares to say that the heart in such preparations reacts as would an intact heart or that every factor can be perfectly controlled?

I cite these objections not to condemn the method, nor to discourage its employment in the analysis of the cardiac mechanisms. On the contrary, I am of the opinion that its employment has greatly enhanced our knowledge of the fundamental laws according to which the heart *can* react. I merely wish to emphasize the possibility that such laws may apply only to special conditions and must always be transferred to the intact circulation with the greatest reserve and caution.

With such reflections in mind, I have recently investigated the ventricular pressure and volume changes during conditions of altered arterial resistance and venous inflow on intact animals, for, in such experiments, in contrast to studies on the heart-lung preparation, it is possible to study what probably *does* happen when the heart reacts to different influences. Both right and left intraventricular pressures were simultaneously recorded by optical manometers. In some experiments the volume changes were also recorded; in others, volume curves were omitted in order to test the same procedures in animals in which the natural pericardial support of the ventricles was maintained.

In seventeen experiments, so far completed, it was found, without exception, that any sudden increase in venous return which increases also the volumes of the ventricles, always promptly elevates the initial tension and pressure-maximum in the right as well as left ventricle. This is illustrated by the

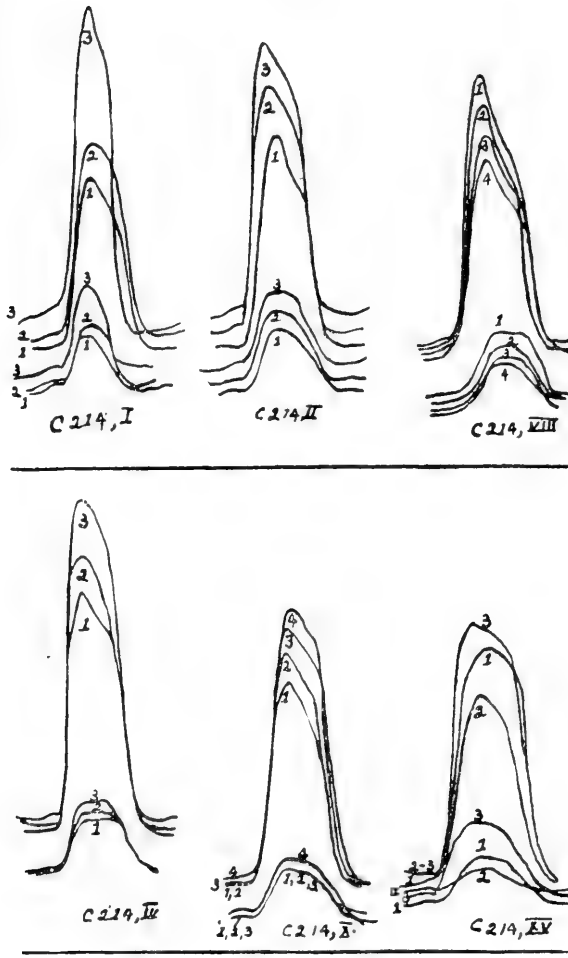

FIG. VII.—Superimposed tracings of right (lower) and left (upper) intraventricular pressure curves, after experiments of author. I, normal as compared with effects during asphyxia; II, normal as compared with saline infusion effects; VIII, normal as compared with decreased venous return after vena cava compression; IV, normal as compared with effects of vaso-constriction; X, as compared with effects of aortic compression; XV, normal as compared with effects of chloral (2) and strophanthin (3).

records shown in Figure 7, II. Curves "1" are normal controls. Fifty c.c. of warm saline solution was then allowed to flow into the external jugular vein in twelve seconds. In other experi-

ments, this had been shown to increase definitely the diastolic volume of the ventricles and augment the systolic discharge in from 2 to 3 seconds. Four seconds after, curves "2" were recorded. Both intraventricular pressure curves show an elevation of initial, as well as maximum pressure. Toward the end of the infusion, the third series of curves were taken; a further elevation of initial and maximum pressures in both ventricles is obvious.

Reduction of the venous inflow produced by clamping the inferior vena cava has precisely the reverse effects on initial and maximum pressure in the two ventricles. This is shown in records labeled as observation VIII. Such changes in initial pressure occur with great promptness when the volume of fluid returned is either decreased or increased. Thus, in observation VIII, "1" shows the normal control, "2," "3" and "4" illustrate the changes taking place during the second, fourth or sixth beats after compression of the vena cava.

When arterial resistance increases either through intense vasoconstriction or mechanical compression of the aorta, the initial pressure is always elevated when it is of sufficient degree to cause a dilation of the ventricles. The details of these changes are illustrated in the series of records shown in IV and X. Observation IV indicates the final results during intense vasoconstriction reflexly induced by stimulating the central end of a divided vagus nerve. Curves "1" are normal controls. While arterial pressure (recorded supplementary) was on the ascent, curves "2" were recorded. At the height of the pressure reaction curves "3" were taken. In both, a considerable elevation of initial pressure is indicated in the left ventricle pressure curves and a relatively smaller increase is discernible in the right ventricle. In observation X are noted the immediate effects of raising the arterial resistance through mechanical compression of the thoracic aorta. Curves "1" are normal, curves "2" represent the pressure changes during the first beat following compression. The pressures in the right ventricle are unaffected. The pressure-maximum increased by virtue of the higher resistance and pressure existing during the contraction process. The initial pressure

has not elevated. Curves "3" show the changes in the third beat after compression. Increased initial tension and pressure-maximum occur in the left ventricle, the pressure in the right still remaining unchanged. Curves "4" represent the fifth beat after compression. Initial pressure and pressure-maximum are further elevated in the left and, for the first time, in the right ventricle also.

Experiments of another order have also been carried out. In these, the ventricular volume curves were recorded on a slowly moving smoked paper; the two intraventricular pressure curves, as before. At the first indication of an increase in diastolic volume (initial length) after slow saline infusion, optical pressure curves were at once recorded. Comparison with normal curves showed that the initial pressure-increase in the right ventricle was never dissociated from an alteration in initial diastolic volume.

This state of affairs obviously holds good only as long as the inherent functions of the cardiac muscle are not excited or depressed. There are many evidences of deviations from this rule; both in the literature emanating from other laboratories and my own. Thus, when the initial pressure becomes elevated to an excessive degree, the intraventricular pressure-maximum no longer increases but becomes lower at the same time that the systolic discharge lessens. So also, when the heart is long distended by a great inflow or is required to react against a very high arterial resistance for a long time its subsequent power of response is reduced. The irritability of the heart may also be depressed or stimulated by chemical agents, in which case the pressure-maximum and systolic discharge are not related to the initial pressure. This is illustrated in observation XV, in which curves "1" again show normal controls. Curves "2" are representatives of pressure changes following the use of chloral hydrate. Initial pressure is greatly elevated in the right, very slightly in the left ventricle. In spite of this, the pressure-maximum is lower in both ventricles. The heart was obviously dilated. Neither increased initial pressure nor increased initial length determines the vigor of the ventricle when the myocardium is depressed. Curves "3" were obtained after subsequent use of

strophanthin. The tension maximum increased above normal in both ventricles—the initial tension remaining unaltered in the left and decreased in the right.

Viewing all the experimental evidence in the light of the more fundamental work of Blix, Hill and others on skeletal muscle, we must be ready to admit that the dynamic efficiency of the ventricle may be fundamentally determined by such factors as initial length, and diastolic surface-volume relations. It is not so evident, however, (except, perhaps, under conditions of very small venous inflow, or where the ventricle has lost its tonus completely) how any increase in diastolic volume (and initial length) can take place otherwise than by the force of an increased initial tension. The ventricles are filled to capacity even under very low auricular pressures. It would seem that any additional increase in volume must necessitate a stretching of the elastic and tonic walls of the ventricle. This requires an increased auricular and increased initial pressure. The pressure required to stretch the walls sufficiently to admit a definite volume increase need not be great, if the tonus is low; but must be considerable, if it is high. The pressure increase is not proportional to the volume increase; but an increase must exist. We may reiterate: While initial length of ventricular fibers and diastolic surface-volume relations may fundamentally determine myocardial efficiency, it is difficult to picture how these factors can be increased except through an increase in initial tension.

III. THE DYNAMICS OF THE CIRCULATION IN HEART DISEASE

The signs and symptoms arising from acute or chronic cardiac disease are the expressions of dynamic consequences which occur when the normal valvular mechanism is impaired or the functional capacity of the ventricular myocardium is affected. As the latter are always concerned more or less in valvular effects, it seems desirable to analyze on the basis of experimental results, how the myocardium becomes abnormal in its function, to consider the factors of safety that are at once called into play, to analyze

how additional compensatory mechanisms gradually develop, and finally, to attempt an answer as to why these mechanisms ultimately fail to accomplish the task for which they were developed.

The Hypodynamic or Inherently Weakened Heart.—Under this heading I mean to catalogue cardiac conditions in which the working capacity of the ventricles has been reduced. It is, I believe, the condition which so frequently follows or terminates severe febrile or infectious processes. Clinically, it is recognized chiefly by the feeble heart sounds (particularly the first) and the small pulse amplitude. The latter has definitely been proven to be caused by the decreased systolic discharge; the enfeeblement of the first sound I[22] have recently shown to be related to and diagnostic of a reduction in intraventricular tension.

It is probable, therefore, that we have, in this hypodynamic heart of the clinic, a condition not unlike that produced by depressant drugs such as chloral, chloroform, etc., and consequently, we may venture an interpretation of the cardiodynamics on the basis of experimental results obtained from the use of such drugs.

The capacity of the ventricle for work is, of course, a function both of pressure and volume, as well as time. O. Frank has expressed it by the integral, $A = \int_{T_0}^{T_1} P.\ V.\ dx$ in which A represents the work; P, pressure; V, volume; T_0, time of opening of semilunar valves; T_1, the time of closure of the semilunars. Owing to the facts that the volume curves of each ventricle cannot be separately recorded and that initial tension is a function both of aortic resistance and venous filling, it has not been found possible to apply this formula in estimating the working capacity of the mammalian heart beating under different conditions. A separate study of the changes in the volume and pressure curves of the ventricles has given us, however, a clue to the essential changes taking place in the hypodynamic heart. Socin,[17] who studied the volume changes, systolic discharge and minute volume of the heart depressed by chloroform, found that such depression expresses itself primarily by a decreased systolic discharge and, in consequence of the inefficient discharge, by a dilation. The

[22] Wiggers: Ach. Int. Med. 24:471, Sept., 1919.

depressed heart retains only to a lesser degree its power of responding to changes in venous inflow or arterial resistance. If, for example, the arterial resistance is increased, the systolic discharge is not maintained as in the normal heart but continues reduced for a long time. This leads to dilation. Again, when the venous pressure is increased, it does not respond with an increased output as the normal heart, but the discharge remains unaffected.

Similar evidences of its inability to respond to increased requirements are shown by studies of the pressure curves. Experiments, not yet completed but well under way, point to the conclusion that, when the heart is acutely depressed by such agents as chloroform, chloral, alcohol, etc., the intraventricular pressure progressively rises less abruptly and to a lower level in spite of the fact that the initial pressure is elevated and the diastolic ventricular volume, to judge from volume curves, is actually greater.

The heart gradually recovers from such effects. This, we are accustomed to attribute to the fact that the chemical action gradually wears off. Pressure curves indicate, however, that this "wearing off" effect is not entirely due to the cessation of a toxic action but involves rather a process of compensation. This seems to occur as follows: As a small quantity of blood is retained during successive systoles, the initial tension and initial distension of the ventricles is greater. When this has gone sufficiently far, the hypodynamic heart reacts to the higher initial tension and the amplitude of the pressure curve again increases. In these depressed hearts, the impression is clearly gained that initial tension fundamentally determines the pressure relations; and present one instance as to why the analysis of the relative importance of initial length, and initial tension, in determining cardiac efficiency is of more than academic interest.

If cardiac depression is more severe, the ventricular pressure is not elevated to normal even if the initial pressure itself is considerably higher. By virtue of the higher initial pressure, the ventricle dilates more and more and the pressures in the left auricle and entire pulmonary circulation have a tendency to become elevated. Marked pulmonary congestion is probably

avoided because the output of the depressed right ventricle is diminished by an amount nearly equal to that of the left. Stagnation of blood in the veins and liver without pulmonary congestion can thus be explained in a logical manner.

If the influences depressing the contractile power of the ventricles are removed, or if they are neutralized by suitable cardiac stimulation, gradual recovery may take place. Such experiments favor the use of such stimulating drugs as digitalis and strophanthin in purely myocardial types of depression.

Cardiac Strain and Fatigue.—Cardiac strain begins when the normal or hypodynamic heart is required to eject its blood against a greater arterial resistance, or, what amounts to the same thing, a higher diastolic pressure. The reactions correspond to those previously analyzed when the arterial resistance is increased experimentally. As a result of the greater load, a small increment of blood remains behind, at once distending the ventricle. As long as the elastic and tonic resistance of the myocardium is not impaired, however, it at once elevates the initial tension. This safety mechanism causes a larger pressure elevation and a restoration of the discharge to normal. The earlier phases of this reaction are undoubtedly beneficial. With the higher pressure developed during the isometric phase goes an intensification of the first sound; and with the closure of the semilunar valves at a higher diastolic level, we get, as has been experimentally demonstrated, an accentuated second sound. As long, therefore, as both sounds remain intensified, the heart is responding by adequate safety mechanisms.

If the factors increasing diastolic pressure operate too rapidly, or if the elevation is continued too long, a second phase of cardiac strain develops. During this stage, as Bruns[23] has shown in the frog's heart, the inherent contractility suffers. In the mammalian hearts, the intraventricular pressure curves do not mount so high and the isometric slope become more gradual, even though there is a progressive dilatation of the ventricle and an increased initial pressure. When this occurs, the second sounds may remain intensified, while the first sound vibrations become reduced

[23] Bruns: Deutsch. Arch. f. klin. Med. 113:179, 1913.

in amplitude. Since the tonic contraction of the cardiac muscle and its elastic resistance is unable for long periods of time to resist the gradually increasing strain, the heart begins to weaken and finally gives way (Bruns). The ventricle then dilates enormously. This marks the onset of cardiac fatigue. Straub's experiments indicate that when this occurs the pressures in the left auricle become greatly elevated and the lungs markedly distended. The right ventricle, in consequence, is compelled to contract against a greater load; it then passes through the same phases of cardiac strain as the left. During the time that dilation of the

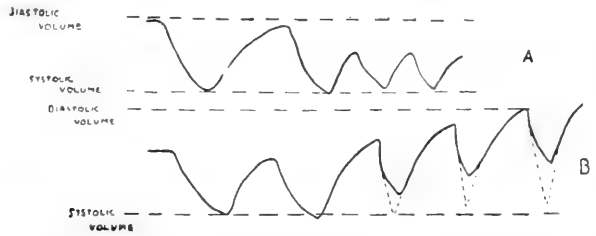

FIG. VIII.—A, upper curves, series of diagrammatic volume curves showing mechanical decrease in diastolic volume when the heart accelerates, according to conceptions of Henderson. B, lower curve showing effect of increasing diastolic volume due to increased venous inflow when tonus remains normal (dotted lines) and when it is reduced (solid lines). Result, is a larger systolic volume in the former, and unaltered discharge in the latter instance.

left ventricle is backing blood into the pulmonary circuit, the efficiently contracting right ventricle adds normal volumes of blood to the pulmonary side, consequently, pulmonary congestion cannot fail to supervene during the second stage of cardiac strain, while there may be no evidence of venous congestion.

Either one of two sequels must follow: the right ventricle may pass to the stage of dilation causing the venous pressure to rise and pulmonary pressure to fall, or new compensatory mechanisms may come into play which help to reestablish normal relations.

Tonus and Dilatation.—These terms are constantly employed by physiologists and clinicians alike, without always a clear conception of what they really imply. When the exposed heart appears large and distended during diastole, we speak of a dilated heart or one having a low tonus. If, on the other hand, the diastolic volume is small, we are apt to speak of tonus as being high. As Patterson, Piper and Starling point out, the state of

distension and tone are not necessarily related "for the volume may be merely determined by the amount of blood entering from the veins." Henderson has shown that the diastolic volume of a heart distended by high venous inflow is necessarily greater than that of a heart which receives only a small venous inflow. Obviously, the diastolic volume of the heart is usually passively determined and in such cases the more dilated hearts are the more efficient; both because the initial and maximum intraventricular pressures are higher, and because the systolic discharge is greater (Fig. 8, A). For the sake of differentiating, let us speak of this as a physiologic dilatation (tonogenic dilatation of Moritz).

Clinically, the term "dilatation" is applied to a condition in which the heart is dilated during diastole while the systolic discharge is diminished; or, perhaps, more precisely stated, when the dilation is not accompanied by a larger discharge. In other words, the heart is dilated during systole as well as diastole; a relation that may be expressed by the volume curves diagrammatically shown in Figure 8, B. Let us hereafter refer to this type as pathological dilatation (myogenic dilatation of Moritz).

Pathologic dilatation is frequently attributed to a failure of cardiac tonus; the physiologic type, to a passive distension in which tonus persists. According to such conceptions, Patterson, Piper and Starling consider the term tonus "as synonymous with the physiological condition or fitness of the muscle fibers and its measure is the energy set free per unit length of muscle fiber at each contraction of the heart." A heart with good tonus will carry on a large circulation and nearly empty itself at each contraction, a heart with defective tonus can eject the same systolic volumes, only when its fibres are lengthened (Fig. 8, B). This is also essentially the conception formulated by Moritz.[24]

While this expresses the end effects of tonus changes, and relates the importance of tonus to cardiac efficiency very well, it does not clearly define the nature of tonus itself, nor does it analyze the mechanisms through which tonus governs cardiac efficiency. To the physiologist, the term "tonus" has come to signify a sort of a sustained partial contraction of muscle tissue

[24] Moritz: Deutsch. Arch. f. klin. Med. 66:349, 1899.

by virtue of which the muscle fibers resist stretching more than they would by virtue of the inherent elasticity alone. According to this conception, the ventricular tonus varies directly as the volume-elasticity coefficient of the relaxed heart, i. e., the ratio of the pressure increase to the volume increase, $\frac{\Delta p}{\Delta v}$.

This relation may be studied after the fashion schematically illustrated in Fig. 9. Let us suppose that, in such a preparation,

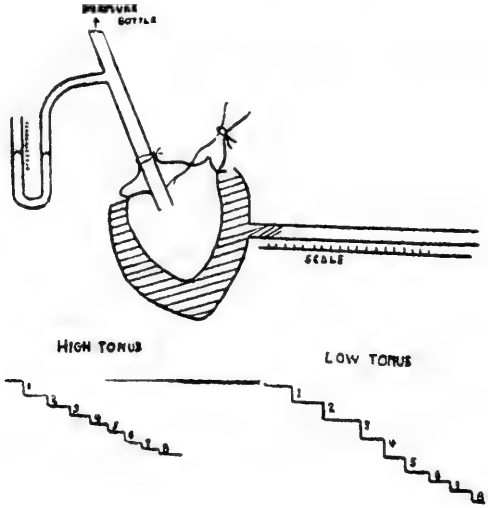

FIG. IX.—Diagram illustrating principle of measuring volume—elasticity coefficient of relaxed ventricles. Lower curves illustrate distention curves in heart with high and low tonus, each step representing an equal increment of intraventricular pressure.

sufficient fluid is admitted into the ventricle to raise the intraventricular pressure by eight equal increments. The volume changes corresponding to each of, say eight, such pressure elevations may then be plotted in steplike fashion. Comparison of curves from ventricles under varying conditions of tonus make it quite obvious that when tonus is low, a much greater increase in volume accompanies a given pressure increase than when tonus is high; or, stated in the reverse, the same volume change is associated with a much greater pressure change when tonus is high than when it is low.

We may now again examine into the reasons why a heart

with deficient tonus is less effective than the normal. Two hearts, distended to equal volumes, would have equal initial lengths. If this is the dominant or only factor determining the power of the heart to respond, we can only assign the decreased working capacity to an impairment of the muscular ability itself. Such is apparently the conception of Starling and his associates. If, however, initial tension is primarily concerned in determining the working capacity of the heart, then the reduced working capacity of the ventricle during atonia may be accounted for by the fact that, at equivalent initial volumes, the initial pressure is lower in the atonic than in the normal heart.

The factors which may modify cardiac tonus have not all been definitely established on an experimental basis. Thus, from the experiments of Socin,[17] it could not be definitely ascertained whether in cardiac depression from chloroform, tonus was also reduced. Bruns,[12] however, was able to show definitely that tonus in the frog's ventricle is reduced when for long periods of time the heart is made to beat a very rapid rate, or compelled to work against increased resistance.

Compensation and Decompensation.—It is the dynamic function of the heart so to adjust its mechanisms that it, at all times, pumps the venous blood received into the systemic system under sufficient pressure to insure a continued capillary flow. As long as the heart does this, the circulation is compensated; when it fails to do so, decompensation occurs. The power of compensation is a physiological attribute of normal muscle tissues and is not necessarily linked with subsequent cardiac hypertrophy. This phase of the compensatory phenomenon may be well illustrated by reference to the acute production of a severe experimental lesion in animals. If, for example, the aortic valves are suddenly rendered incompetent, it will be found that the aortic diastolic-pressure not only falls at once, but that the systolic pressure remains normal or rises above normal with the very next beat. The mechanisms through which this is accomplished operate somewhat as follows: With the first diastole, a small volume of blood regurgitates back into the ventricles. This not only distends the ventricles but elevates the initial tension. Conse-

quently, during the next and every subsequent beat, not only the tension-maximum, but also the volumes ejected during systole are greater. Compensation for valvular defects then resolves itself into an increase in diastolic volume and initial tension which causes the heart to react, at once, by larger pressure curves and larger output.

Under what conditions does such immediate compensation fail to take place? Two suggest themselves: (1) If the tonus of the heart muscle, as defined, is low, augmented volumes may be accommodated within the ventricle without a proper elevation of initial tension. When this happens, the pressure-maximum reached within the ventricles and aorta are both lower and the discharge is actually decreased. (2) If the reserve power of the normal ventricle is exceeded, or if, through depressing agents, the normal reserve power is reduced, then also, decompensation supervenes. This necessitates an interpretation in more precise physiologic terms of the phrase "reserve power."

We have seen that every increase in diastolic volume and initial tension causes not only a larger systolic discharge but a higher pressure-maximum within the ventricles as well (Fig. 7). To this, as it has been experimentally shown, there is, however, a limit, for, if the initial pressure increases more and more, there comes a time when the pressure-maximum begins to decrease. Then the systolic discharge also decreases. The initial pressure at which this turning point occurs may be taken as the index of the reserve power of the ventricles. Whenever, therefore, the increase in initial pressure occasioned by a valvular defect rises above this point, the efficiency of ventricular contraction diminishes and decompensation begins. This safety mechanism whereby the ventricle is capable of responding at any moment's notice to larger initial tension, undoubtedly explains why decompensation does not, as a rule, occur in valvular lesions for many years, and that patients remain quite unaware of valvular disturbances which may be very marked.

The initial pressure at which the heart no longer responds with more vigorous beats and normal systolic discharge varies, not only in different animals, but in the same heart, e.g., when its

blood supply is altered or when the heart muscle has been submitted to toxic depression or long continued stain. We have in this a clear explanation as to just how the condition of the myocardium finally determines whether compensation or decompensation takes place. For years, experiments on artificial circulation machines (Marey,[4] Moritz,[25] etc.) had demonstrated that, whenever left heart valvular lesions occur, there is always a physical tendency for blood to dam back toward the right side, thus increasing pulmonary and right ventricular pressures. On the basis of such physical experiments, clinicians have long explained the pulmonary congestion and venous stasis observed in cardiac cases on the so-called "back pressure theory." It was, therefore, surprising that practically all experimental investigations of the various heart lesions (MacCallum and McClure,[26] Straub,[7] etc.) show that "back pressure effects" occur very seldom in lesions acutely produced in normal hearts. How are these observations to be interpreted? The physics of the body circulation is not different from that of artificial circulation machines. Back pressure effects should be and, as a matter of fact, would be produced, were it not for the immediate compensatory reactions called into play. When, in animals or in patients, this compensatory mechanism (i. e., the ability to respond to increased initial tension and volume by equal discharge and higher pressure-maximum) is lost, decompensation sets in. Then, and then only, "back pressure effects" take place.

[25] Marey: La Circulation du Sang 16:136, 710.

[26] MacCallum and McClure: Johns Hopkins Hosp. Bull. 17:260, 1906; 22:197, 1911.

NEWER ASPECTS OF SOME NUTRITIONAL DISORDERS*

DR. ALFRED F. HESS

Professor of Clinical Pediatrics, New York University and Bellevue Hospital Medical College

ONE of the most novel medical conceptions is that serious diseases or functional disorder may be occasioned by a mere lack of certain constituents in the dietary. Until recently we were wont to associate tissue damage or functional disturbance solely with the introduction of some harmful foreign substance—chemical or bacterial—into the body. It is not only remarkable but also creditable that a concept so revolutionary should have gained wide acceptance in so short a time, not only among the medical and scientific world, but among the public at large. The first to bring forward convincing evidence in favor of this view was Eijkman[1] who noted in the course of his experiments in Java that fowl fed on decorticated rice became paralyzed and developed symptoms resembling beriberi, which disappeared when rice polishings or their alcoholic extract were added. The subject slumbered for some fifteen years when, less than a decade ago, Hopkins[2] established it on a scientific basis by demonstrating that animals were unable to live on a dietary composed of casein, starch, lard, water and a mixture of inorganic salts, after these ingredients had been carefully purified, but that this diet could be rendered adequate merely by adding a small amount of a natural food—a few cubic centimetres of milk. It will be noted that the new path was blazed as the result of empiric observation as well as carefully planned scientific investigation, and further-

* Delivered January 15, 1921.

[1] Eijkman, C.: Eine beriberi aehnliche Krankheit der Huehner, Virchows Arch. f. path. Anat. 148:523, 1897.

[2] Hopkins, F. G.: Feeding Experiments Illustrating the Importance of Accessory Factors in Normal Dietaries, J. Physiol. 44: 425, 1912.

more, that as has happened so frequently in the past, alert empiricism outran and prepared the way for the more carefully planned laboratory experiment. Today the fact that there are deficiency diseases is taught to children in the schools, and vitamins are bandied about in the advertising pages of the daily papers, and are the proper concern of the up-to-date mother. This rapid diffusion of scientific knowledge, despite the interruption of the war, furnishes a striking illustration of present-day alertness in connection with topics affecting personal health and vigor.

No doubt the disorders brought about by a deficiency of the vitamins or accessory food factors have occurred for centuries. To a considerable extent, however, they must be regarded as typically modern disorders. Viewed as a group they are a consequence of our unnatural mode of life and peculiar civilization, of the growth of immense cities housing millions of people, who are dependent on perishable foodstuffs transported from a great distance. To even a greater extent they are the product of countless ingenious methods devised mainly to render food stable —drying, heating, the addition of preservatives—most of which accomplish their objects, but incidentally rob the food of one or more of its essential constituents. In a measure these nutritional disturbances are a consequence of the supreme domination of the bacterial point of view, of the ever present dread of infection and solicitude to protect ourselves against contaminated foodstuffs. This fear has led to the demand for a more or less complete sterilization of foods, and to a preference of foodstuffs whose unsullied whiteness lends them the appearance of purity— as in the case of polished rice, and highly milled flour.

The current view associates deficiencies of the various vitamins with specific disorders, for example, with beriberi or with scurvy. Now, although it is quite true that such diseases demonstrate conclusively the absolute necessity of certain constituents in our dietary, it is likewise true that clear-cut disorders should not be regarded as the most common or important result of food deficiencies. It should be realized that a lack of these essential food factors generally does not bring about typical pathologic

states, but obscure alterations of nutrition, ill defined functional disabilities, which cannot be characterized or even recognized as disease. It is such incomplete, larval forms of the deficiency disorders to which physicians will have to address themselves.

Nor should the domain of the deficiency disease be restricted to the narrow confines of disturbances brought about by a lack of vitamins. In a broader sense it includes malnutrition due to an insufficiency of any food constituent which is essential to normal metabolism. The peoples of the Central Empires, for example, as the result of a great lack of meat, milk, cheese and eggs, were compelled to subsist during the war on a dietary which was deficient in phosphoric acid as well as in one or more of the vitamins.

Many observations lead to the conclusion that these disorders are not limited to man, but to a large extent affect the animals which man uses for food. It has been found in Victoria, for example, that cattle raised on certain pastures develop paralysis and other infirmities which can be cured by fertilization of the soil. In the United States in some areas it is impossible to maintain cattle in good condition until the forage is improved by mineral or animal fertilizers, which illustrates that a deficiency in plant tissues leads to nutritional disorder in animals. Recently Hart, Steenbock and Humphrey[3] have confirmed these observations by careful experiments which showed how the mere addition of calcium to the fodder of cows prevented the birth of premature, weak or dead calves. Indeed, the extensive investigations of Forbes showing that cows producing large amounts of milk, and fed common winter rations, undergo constant losses of calcium, magnesium and phosphorus from their skeletons, suggest that large numbers of milch cows are suffering from a deficiency disease. These chemical analyses recall Hanau's report[4] of almost thirty years ago, to the effect that the bones of pregnant women, who had enjoyed apparent health, frequently were the

[3] Hart, E. B.; Steenbock, H., and Humphrey, G. C.: Influence of Rations Restricted to the Oat Plant on Reproduction in Cattle, Research Bull. 49, Agric. Exper. Station, Univ. Wisconsin, 1920.

[4] Hanau, A.: Ueber Knochenveraenderungen in der Schwangerschaft, Fortschr. d. Med. 10: 237, 1892.

site of lesions resembling osteomalacia—an interesting observation that might be substantiated during life by means of roentgenologic examinations.

SCURVY

The most clear-cut and sharply defined deficiency disease is scurvy. In fact, it is the only nutritional disorder brought about by inadequacy of diet—whether of vitamin, of a definite chemical substance, or of calories—which is associated with characteristic pathologic alteration. For we must bear in mind that the nerve degenerations of beriberi are not typical or diagnostic as are the bone lesions of scurvy. The latter disorder, therefore, is preeminently qualified to serve as the prototype of this class of diseases. The clinical picture usually called to mind by the word "scurvy" is that of an individual afflicted with a severe, acute disease; either an adult with bleeding, fungous gums, hemorrhagic eruption and painful gait, or a pale, unhappy infant, with gingival hemorrhages, and tenderness or swelling of one or both lower extremities. This is the classic text-book picture, which should not, however, be regarded as the ordinary or prevalent type of scurvy, either in adult or infant. The more common form is far more subtle in its manifestations, as is true of other nutritional disorders. In the adult it is evidenced by a lack of physical or mental vigor, vague pains suggesting rheumatism, an increased susceptibility to infection—conditions often impossible to diagnose when occurring sporadically, but conclusive when scurvy pervades a large group of individuals. Such scurvy was noted during the War of the Rebellion among the Northern troops, being referred to as a "scorbutic taint," and is mentioned in the recent report of the British troops in Mesopotamia. It has been described by me in relation to infants,[5] and during the war by physicians in Vienna who had charge of child-caring institutions.[6] They noted, in addition to infants suffering from manifest scurvy, a far larger number of what may be termed "subacute" or

[5] Hess, A. F.: Subacute and Latent Scurvy: The Cardiorespiratory Syndrome, J. A. M. A. 68: 235 (Jan. 27) 1917.

[6] Tobler, W.: Der Skorbut in Kindersalter., Ztschr. f. Kinderh.

"latent" cases with the characteristic muddy complexion, lack of appetite, stationary weight and fretful disposition. That this syndrome is truly scorbutic has been proved repeatedly by the miraculous improvement which follows the addition of an antiscorbutic to the dietary. From our knowledge that about six months of the inadequate diet is required to bring about definite clinical manifestations, it follows that there must be a mild or latent type of scurvy and that this form must comprise the majority of the cases.

I shall not weary you with a review of the sypmtomatology of scurvy, but rather consider briefly the tissues and bodily functions which are particularly affected when the antiscorbutic food factor is lacking in the dietary. This vitamin is probably needed for the normal functioning of all the cells of the body—if we may interpret in this sense the general loss of mental and physical vigor—however its lack is evidenced in particular directions; in a failure of the integrity of the endothelium of the blood vessels; in a disintegration of the structure of the bones; in various disturbances of the circulatory system. It may be of interest to discuss briefly these three conditions, as their occurrence must be closely associated with the function of the antiscorbutic vitamin.

The lesion of the lining of the blood vessels is one of the most characteristic signs of scurvy; it is the cause of the hemorrhage of the gums, of the petechiæ in the skin, of the subperiosteal hemorrhage, the hematuria, and all the other hemorrhagic manifestations which have frequently led to the inclusion of scurvy among the group of hemorrhagic diseases. The coagulability of the blood is almost normal in this disorder, the escape of the blood from the vessels being due to a weakening of their walls, or to a lesion of the endothelial cells or their cement substance. Applying a tourniquet to the upper arm (the "capillary resistance test"), thus subjecting the vessel walls to additional strain, will generally demonstrate this weakness, causing the appearance of numerous petechiæ on the forearm. A similar weakness of the vessel walls does not occur in beriberi, or in any clinical condition attributed to a lack of vitamin.

It is unnecessary to dwell on the fact that the bones are particularly vulnerable to a lack of the antiscorbutic factor. For decades attention was centered to such a degree on the bones that clinicians as well as pathologists gave little heed to manifestations occurring in other organs.

The association of circulatory disturbances with "latent" or "subacute" scurvy is of particular interest as, until recently, these symptoms have been overlooked. They furnish a clinical link between scurvy and beriberi, the deficiency disease attributed to the lack of the so-called water-soluble vitamin. Frequently one of the earliest signs is tachycardia, a heart beat of 140 or 150 in an infant. But a still more noticeable and characteristic sign is the marked instability of the pulse rate, an increase of 20, 30 or 40 beats to the minute on the least exertion or from a slight rise in temperature. This tachycardia is similar to that of exophthalmic goiter, the electrocardiogram showing merely an exaggerated T-wave. Accompanying this tachycardia there is generally a polypnea—respirations mounting to 40, 50 or 60 to the minute. These symptoms may be termed "the cardiorespiratory phenomenon" of scurvy. That it is truly scorbutic may be deduced from the fact that it yields promptly to antiscorbutic treatment. Its occurrence points to an involvement of the nervous system, and at least to a functional relationship between this vitamin and nerve tissue, thus illustrating the inaccuracy of the appellation "antineuritic vitamin" as applied to the beriberi vitamin.

Another scorbutic symptom is enlargement of the heart, especially of the right heart, a lesion which has been considered typical of beriberi. For many years this lesion was overlooked in scurvy, owing to the fact, as stated, that attention was narrowly focused on the bones, an oversight which is strikingly evident in reviewing necropsy protocols. It may be noted that Erdheim[7] of Vienna recently published a paper with the significant title of "Das Barlowherz," in which he describes thirty-one necropsies of infantile scurvy in which the heart was found enlarged in almost every instance.

[7] Erdheim, J.: Ueber das Barlowherz, Wien. klin. Wchnschr., 1918, p. 1293.

In concluding this summary of the relation of scurvy and its vitamin to the circulatory system, passing attention should be called to oliguria, the diminished secretion of urine in the course of scurvy, a symptom at once alleviated on administering an antiscorbutic. This sign is still more common in beriberi.

NATURE OF VITAMINS

As is well known, the exact chemical structure of a vitamin is as yet a mystery. This lack of knowledge has led to skepticism, even to the point of doubting the very existence of the vitamins. This attitude is strange, in view of the fact that for almost a generation we have become quite accustomed to conceding the existence of factors which we are unable to isolate chemically. We know quite as much about the chemical nature of the vitamins as we do of complement, hemolysin or immune bodies—substances which have gained general recognition and are admitted to the select company of scientifically established entities. Not only the nature of the vitamine but also their mode of action is unknown: whether they exert their effect directly on the tissues, or indirectly, as has been suggested, through a hormone action. It seems clear that man cannot manufacture them, or at most can do so to a limited extent—insignificant from the standpoint of his well-being. We are therefore entirely dependent on our food supply for these essential factors. Nor has it been shown that any other of the higher animals possess this ability. Lower forms of animal life, seem to be able to elaborate vitamin, and plant cells such as the yeast cell, possess this faculty to a high degree. Not only are we unable to manufacture these vitamins, but it is probable that we are unable to store them to any great extent. A series of experiments planned to investigate this question, and described in detail elsewhere,[8] led to the conclusion that at least guinea-pigs are unable to store the antiscorbutic vitamin. In other words, we are leading a precarious hand-to-mouth existence in regard to food factors which are essential not only to our health but also to our lives.

[8] Hess, A. F.: Scurvy, Past and Present, Philadelphia, J. B. Lippincott Company, 1920.

ANTISCORBUTIC VEGETABLES

It is hardly an exaggeration to state that in the temperate zones the development or nondevelopment of scurvy depends largely on the potato crop. In Ireland, when the potato has failed, scurvy has developed. The same thing has been true in Norway. To a minor degree this happened in 1914 in various localities in the United States, when the potato crop was inadequate. This is attributable in part to the fact that the potato is an excellent antiscorbutic, but to a greater extent because it is consumed during the winter in amounts that exceed the combined total of all other vegetables. The great nutritional value of the potato has not been explained. Its protein is stated to be of inferior quality, and it is poor in the water-soluble and in the fat-soluble vitamins. Nevertheless, the practical dietic experience of nations and the prolonged investigations of Hinhede prove that it is a food of exceptional value.

One of the recent advances in the study of scurvy has been a more exact appreciation of the antiscorbutic value of foods, an appraisal of vegetable and animal foodstuffs from a quantitative standpoint. This has led to some surprises; for example; that the lime, which has been time honored as the most potent of antiscorbutics, is not comparable in this respect to the lemon or the orange. We have learned also to appreciate the value of the swede and of the tomato. But of still greater importance is the realization that any categorical statement of the relative value of antiscorbutic foods must be accepted with qualifications. *Foods should not be considered as chemical entities.* A lack of understanding of this fact has led to nutritional disease in man, and to confusion in investigations on animals. For example, a vegetable such as the carrot may possess moderate or very little antiscorbutic power, depending on attendant circumstances. If it is old, it is poor in the antiscorbutic vitamin, whereas if it is young and succulent, it is far richer in this factor. We had a surprising experience some years ago when guinea-pigs developed scurvy in spite of a ration which included large amounts of carrots such as are ordinarily fed laboratory animals. Experiment readily showed that 35 gm. a day per capita of these carrots

was insufficient to protect a guinea-pig, whereas the same quantity of a young carrot sufficed. Furthermore, it is not immaterial whether the vegetables are freshly plucked or whether they are stale, and it is quite possible that antiscorbutic potency depends to a certain extent on the composition of the soil; in other words, that the vegetable may in turn suffer from a vitamin deficiency disease. Such being the case, the influence attributed to climate in the causation of scurvy—for, as is well known, certain countries have always been associated with scurvy—may be due partly to the effect of the soil on the vegetation. Therefore, in rationing individuals or groups, the quality as well as the quantity of antiscorbutic foodstuffs must be considered.

ANIMAL FOODS

Similar qualifications exist in regard to animal foods. For some years there has been marked divergence of opinion as to the antiscorbutic value of milk. This is an important question, as milk constitutes the basal diet of infants during the first year of life, and constitutes frequently their sole antiscorbutic supply. The conflicting opinions of various investigators have been reconciled recently and the results of those who believed milk to be poor as well as those who believed it rich in this vitamin have been substantiated. Its potency depends almost entirely upon the fodder of the cow. We should long ago have established this fact, fortified by our knowledge that animals are unable to synthesize the vitamins. Hart, Steenbock and Ellis,[9] Dutcher and his associates,[10] and Hess, Unger and Supplee[11] have all reported similar results. In our experiment, cows that had been for a period of three weeks on fodder, which was almost completely

[9] Hart, E. B.; Steenbock, H., and Ellis, N. R.: Influence of Diet on the Antiscorbutic Potency of Milk, J. Biol. Chem. 42: 383 (July) 1920

[10] Dutcher, R. A.; Eckles, C. H.; Dohle, C. D.; Mead, S. W., and Schæfer, O. G.: The Influence of Diet of the Cow upon the Nutritive and Antiscorbutic Properties of Cow's Milk, J. Biol. Chem. 45: 119, 1920.

[11] Hess, A. F.; Unger, L. J., and Supplee, G. C.: Relation of Fodder to the Antiscorbutic Potency and Salt Content of Milk, J. Biol. Chem. 45: 229, 1920.

devoid of antiscorbutic vitamin, produced a milk that was almost devoid of this factor, although of normal caloric value and adequate in its fat, protein and carbohydrate content. Such results may well have far reaching dietetic significance; they raise the question whether "winter milk" supplied by stall-fed cows is a well balanced and complete food. It is quite possible that it may become part of dairy inspection to note the adequacy of the fodder as well as the sanitary conditions. Human milk no doubt also varies according to the nature of the woman's food, and in some instances is deficient in antiscorbutic vitamin, owing to eccentricities of diet or to poverty. During the winter months this may at times exert its influence on the nutrition of the child. In closing this brief consideration of the intrinsic variations of vitamin in animal tissues, I should like to suggest that the blood from which the milk is elaborated may also vary in its antiscorbutic content, and that from this standpoint it should not be regarded as a chemical entity.

FACTORS TENDING TO DESTROY THE VITAMIN

To understand the etiology of scorbutic malnutrition it is important to know the antiscorbutic value of natural foodstuffs; but it is equally important to appraise correctly the factors that tend to destroy the vitamin in these foodstuffs. Until recently this problem seemed very simple. The subject was summed up by the statement that foods which have been dried, heated to a high degree, or canned, lose their vitamin content and induce scurvy. The ravages of scurvy in the mercantile marine and in the navy, in the days of sailing vessels, seemed a convincing demonstration of the deleterious effect of preserved food. The matter, however, is not so simple, and recent investigations have proved the fallacy of these generalizations. In regard to the effect of heat, it has been shown that the duration of the heating process is of greater importance than the degree of temperature to which the food is subjected. For example, milk that has been heated to a temperature of 145 F. for thirty minutes has lost more of its antiscorbutic potency than milk that has been raised to 212 F. for a few

minutes. This result confirms clinical experience that scurvy occurs more frequently on a diet of pasteurized than on one of boiled milk. It has been shown also that the reaction of the medium is of importance in regard to resistance to heating—that substances which are acid, such as orange juice or tomato juice, retain their potency in spite of subjection to high temperatures.

Our views on the effect of the dehydration of foods have swung back and forth on insufficient evidence. For centuries it was known empirically that dried vegetables possessed practically no antiscorbutic virtue, as demonstrated in many wars, including our War of the Rebellion. Nevertheless, in the recent World War dried vegetables were again relied on as antiscorbutics. They proved to be the greatest cause of scurvy in the Central Empires. In this country the conception that dried vegetables are the nutritional equivalent of the fresh nearly led to their extended use and general adoption for our army. But although vegetables have not yet been dried by a process which enables them to retain their antiscorbutic vitamin, we must not infer that desiccation per se destroys this factor, as dried orange juice or tomato juice retains almost all of its antiscorbutic value. Nor is this resistance dependent solely on the acid reaction of these foods, for milk, dried by the Just roller process (by which it is subjected to 230 F. for a few seconds) loses little of its potency. Evidently, drying does not necessarily destroy the sensitive antiscorbutic factor.

We should also maintain an attitude of open-mindedness in regard to the effect of canning, commonly regarded as absolutely destructive of this vitamin. In general, this view is sound; but animal experiments as well as clinical tests have proved that this rule has exceptions—that tomatoes may be canned and that milk may be both dried and canned, and yet preserve its antiscorbutic quality. Indeed, we found this to be true of dried milk which had been canned and kept for over a year at room temperature; an astonishing result, considering that such treatment involves subjection to almost all the influences commonly associated with the destruction of this vitamin—drying, heating to a temperature above the boiling point in a neutral or slightly alkaline medium,

canning, and finally the deteriorating influence of age.[12] In view of these experiences, the statement of the British Medical Research Committee to the effect that foods lose their antiscorbutic vitamin after having been dried or tinned requires qualification. The stability of dried milk cannot be attributed, as we at first supposed, to its low moisture content (less than 3 per cent.), as sweetened condensed milk, containing more than three times as much water, was found also to retain the larger part of its antiscorbutic factor.

EFFECT OF OXIDATION

Such irregular and contradictory results suggested the action of some other destructive agent. We were led to believe that oxidation might be a harmful factor, and undertook experiments to investigate this question.

A Typical Test.—Four cubic centimetres of a normal solution of hydrogen peroxid was added to a liter of raw milk, which was then placed in the incubator over night. Eighty cubic centimetres per capita daily, in addition to oats and straw, was fed to a series of guinea-pigs. The animals promptly developed scurvy. Indeed, they manifested signs of this disorder as quickly as when fed milk that had been autoclaved for one hour at 115 C. Cure was accomplished by adding orange juice to the dietary. Evidently the antiscorbutic vitamin was almost completely destroyed by this small amount of hydrogen peroxid. Another experiment showed that orange juice subjected to oxygen had lost a definite degree of its potency, so that an increased quantity was required to cure scorbutic guinea-pigs.

These investigations indicate that oxidation destroys the antiscorbutic vitamin and must be considered in the etiology of scurvy.[13]

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[12] In this respect, however, it should be borne in mind that there is an essential difference between a food which is of an alkaline or neutral reaction in its natural state, and one which has been rendered so artificially; for instance, orange juice rapidly loses its antiscorbutic vitamin after it has been made faintly alkaline, whereas the potato, in spite of its natural alkaline medium, retains this vitamin throughout the winter.

[13] These results were referred to in a discussion of the vitamins at the meeting of the British Medical Association (Cambridge, July 1, 1920). At this session Hopkins also reported that the fat-soluble vitamin is destroyed by oxidation.

Let us in a few words reconsider the antiscorbutic value of milk from this point of view. Dried milk may retain its antiscorbutic virtue, in spite of drying, canning and aging, owing to the fact that it is well packed and hermetically sealed. It loses its potency after it is exposed to the air. When we refer to the deleterious effect of aging—a vague term—we may well be alluding to oxidation. Sweetened condensed milk, which we found to contain antiscorbutic vitamin, is zealously protected from access of air in the course of its manufacture, not for fear of oxidation or destruction of any of its food constituents, but to avoid the danger of bacterial contamination. It is probable that oxidation plays a rôle in the partial destruction of this vitamin in the pasteurization of milk; this seems the explanation of an experience referred to in 1915: the decided difference in the production of scurvy between milk which had been pasteurized in the home and that which had been pasteurized commercially. It may also account for the clinical results of Variot and others, who have repeatedly stated that they fed thousands, indeed, tens of thousands of infants on sterilized milk, and never encountered cases of scurvy; their milk was sterilized in hermetically sealed bottles. Bearing the factor of oxidation in mind may make it possible so to alter the process of manfacture or of the preservation of foods as to increase their antiscorbutic content, and render them more nearly the equivalent of the fresh food.

The deleterious influence of apparently unimportant processes in industrial methods warns us to proceed cautiously in the handling of foods, and not to concentrate our attention too narrowly on the bacterial dangers, for even some slight mechanical manipulation may damage and denature.

RICKETS

We are all aware of a renewed interest in another nutritional disorder affecting primarily the health of children, namely, rickets. This awakening closely followed the recent activity in the study of scurvy—always regarded as a closely allied disorder

—and has been further stimulated by the remarkable outbreaks of rickets and osteomalacia in the Central Empires. Today we find clinicians and laboratory investigators in England, Germany, Austria and the United States endeavoring to shed light on the etiology of this disorder, which Glisson described so vividly more than 250 years ago. Rickets is the most common nutritional

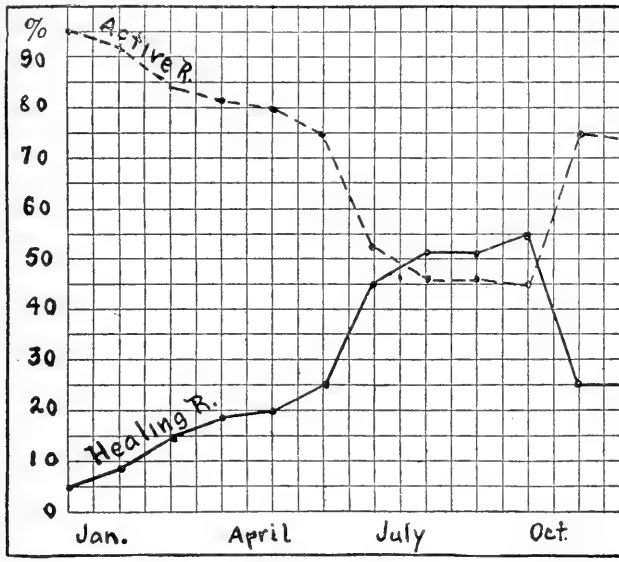

CHART I.—Result of microscopic study of the bones of 386 consecutive necropsies on infants: marked decrease of active rickets accompanied by marked increase of healing rickets during the summer months.

disease occurring among the children of the temperate zone, fully three fourths of the infants in the great cities, such as New York, showing rachitic signs in some degree. Schmorl's pathological studies present evidence that this percentage is still higher when we include cases of latent rickets which can be diagnosed only by the microscope. Furthermore, rickets has the distinction of being the most frequently overlooked disorder of childhood—an important omission, in view of the fact that we possess an efficient agent for its cure.

Broadly considered, there are two main theories as to the

etiology of rickets: the dietetic and the hygienic. It would lead too far afield to discuss the respective merits of these theories. It is my opinion that rickets is primarily a dietetic disorder, but that hygienic factors, such as lack of sunlight, poor ventilation, crowded quarters, and infection, are important contributory influences, far more important than in the case of scurvy. That climate is not the determining etiologic factor is amply proved by the recent experiences of Europe, where rickets developed during the war in almost epidemic form. For example, Dalyell[14] reported from Vienna that, in one community which included many breast-fed infants, rickets was diagnosed in 50 per cent. of the infants at 5 months, and in 100 per cent. at 9 months of age. Davidsohn[15] has emphasized the great increase of severe cases in Berlin during the year following the armistice. This increment occurred despite the fact, shown by an analysis of some thousands of cases, that at the beginning of the war 40 per cent. of the babies were nursed for more than two months, whereas in 1918 more than 50 per cent. were nursed for a similar period.

I believe that I may safely state that today attention is centered on the rôle of the vitamins in relation to the etiology of rickets, and specifically on the fat-soluble vitamin. As the result of the investigation of Mellanby on dogs and the acceptance of his results by the Medical Research Committee of Great Britain, many regard it as an established fact that the fat-soluble vitamin is synonymous with the antirachitic vitamin. About a year ago Dr. Unger and I expressed the opinion that although this vitamin may be a factor in the etiology of rickets, it is not the dominant factor in its pathogenesis.[16] The conclusion was based on a clinical study carried out in an institution for children. As this theory of etiology is the paramount one at the present time, I shall waive other aspects and discuss it in the

[14] Dalyell, E. J.: The Present Position of the Vitamines in Clinical Medicine, Brit. M. J., July 31, 1920.

[15] Davidsohn, H.: Die Wirkung der Aushungerung Deutschlands auf die Berliner Kinder, Ztschr. f. Kinderh. 21: 349, 1919.

[16] Hess, A. F., and Unger, L. J.: The Clinical Role of the Fat-soluble Vitamin: Its Relation to Rickets, J.A.M.A. 74: 217 (Jan. 24) 1920.

light of my experience, which embraces a period of two and a half years, and a careful observation of about 150 cases. My opportunity for a clinical study has been exceptional, as the children were in a model institution, where the diet was prepared in a central kitchen, and all the conditions were uniform and capable of control. Furthermore, I was sure that the infants received a diet adequate in calories and in other food factors. It is only under similar conditions that studies on chronic nutritional disorders can be carried out.

Time will not allow a detailed review of these observations, which will be reported at another time. It may, however, be of interest to summarize the results of two groups of cases, one which received a "fat-soluble minimal" diet and the other a full quota of milk.[17] Among six infants who were given a diet which was generous in every respect excepting in fat-soluble vitamin, a diet comprising adequate calorific value, a full amount of the water-soluble and antiscorbutic vitamins, and an adequate salt mixture, after a period of more than six months only one showed rachitic signs by physical examination or by the röentgen ray. For, as many no doubt know, the course of this disorder can be studied by means of röentgenograms, and its development or cure thus visualized. Röentgenography, which has been employed extensively abroad, and by Phemister[18] and by Howland and Park[19] in this country, has formed part of our monthly routine examination for the last year.[20] This procedure has great value in the investigation of rickets, and no doubt will aid in elucidating some of its perplexities. As stated, one of these six infants receiving a minimal amount of fat-soluble vitamin in

[17] The "fat-soluble minimal" diet consisted of 60 gm. of dried skimmed milk, 30 gm. of sucrose, 30 c.c. of cottonseed oil, orange juice, autolyzed yeast and wheat cereal. In some cases the oil was discontinued for over six months, and an increased quantity of cereal substituted.

[18] Phemister, D. B.: The Effect of Phosphorus on Growing, Normal and Diseased Bones, J.A.M.A. 70: 1737 (June 8) 1918.

[19] Howland, J., and Park, S. A.: Some Observations on Rickets, Arch. Pediat. 37: 411, 1920.

[20] Hess, A. F., and Unger, L. J.: Dietaries of Infants in Relation to the Development of Rickets, Proc. Soc. Txper. Biol. & Med. 17: 220, 1920.

the dietary—only so much as was included in the equivalent of 20 ounces of a dried skimmed milk—showed signs of rickets after a long period of observation. In one case, which was observed for eighteen months, rickets existed at the onset and disappeared on this diet.

At the same time the development of rickets was followed in infants who were receiving daily from 24 to 32 ounces of raw or pasteurized milk. Surely this amount should suffice to protect against a disorder, were its occurrence dependent on the fat-soluble vitamin. Among this group, numbering twelve, who were receiving a dietary rendered adequate by the addition of orange juice, autolyzed yeast, and cereal (for babies over 6 months of age), six developed rickets. That this disorder was truly rickets was proved by its rapid subsidence on the administration of cod liver oil, as shown by physical and röentgen-ray examination. The inference would seem to be that cod liver oil, which is regarded as the prototype of the fat-soluble vitamin, must differ not merely quantitatively but also qualitatively from milk fat. This view is strengthened by metabolism experiments of Schabad, Orgler[21] and others, which show that although cod liver oil almost invariably causes calcium retention in cases of rickets, the substitution of large amounts of milk in the dietary leads to a negative calcium balance. Evidently the fat-soluble vitamin, as it exists in milk, is not the antirachitic factor; neither will a large amount of milk protect against rickets, nor a small amount lead to its development.

In passing, it may be of interest to refer to an investigation of the diet of the negro mother carried out a few years ago by Dr. Unger and myself[22] in a negro district of New York. As is well known, rickets is far more frequent among negro infants in the large cities of the North than among those of any other race, occurring in marked degree in fully one third that are breast-fed. We came to the conclusion that the main defect and

[21] Orgler, A.: Zur Theorie der Lebertranwirkung, Jahrb. f. Kinderh. 37: 459, 1918.

[22] Hess, A. F., and Unger, L. J.: The Diet of the Negro Mother in New York City, J. A. M. A. 70: 900 (March 30) 1918.

the chief variation in the dietary, compared to what they had been accustomed to at home in the West Indies, was a lack of fresh vegetables and fruits, and an excess of carbohydrates. Last spring and fall Dr. Gertrude McCann carried out a similar investigation in this district and came to the same conclusion. This deficiency of fresh vegetable food, accompanied by a high incidence of rickets, is worth noting.

THE EFFECT OF "SEASON"

A remarkable phenomenon noted by Kassowitz years ago, and one which has not been sufficiently emphasized, is the marked seasonal incidence of rickets; its increased occurrence and intensity in the spring, and tendency to fall to its lowest level in the late summer or autumn. In the course of two years' observations, this fact stood out both winter and summer in bold relief; in August and September, rickets almost disappeared in the institution. Not only the clinician, but also the pathologist, is well aware of this seasonal augmentation and diminution; Schmorl's[23] study of some 386 cases brings it out admirably. So definite is this occurrence that any theory which attempts to explain rickets must satisfactorily interpret this remarkable seasonal variation in its incidence. Pellagra, tetany, keratomalacia, and to a less extent beriberi, are associated with a similar variation. The marked increment of rickets in the spring was attributed by Kassowitz to prolonged indoor confinement of the infants throughout the winter, and was the basis of his "domestication" theory. It may, however, be due to a change in diet, not that the infants are given different food, but that the milk in the late spring and summer, when the cows are on pasture and no longer stall-fed, differs from that of the winter. The nature of this difference is obscure. This interpretation does not exclude the beneficent effect of the improved hygienic conditions which come about in the late spring.

[23] Schmorl, G.: Die pathologische Anatomie der rachitischen Knochenerkrankung, Ergebn. d. inn. Med. u. Kinderh. 13: 403, 1914.

COD LIVER OIL

Happily, we have a drug which, if given in sufficient amount, cures rickets. Cod liver oil has been used therapeutically for almost 100 years, but even today it has not been accorded its proper place in therapy. It is recognized as a drug which benefits nutrition, but the fact that it has unequaled value in the prevention and cure of rickets is hardly realized. Some three

Case	Without C L Oil	With C L Oil
1	+0.060	+0.175 +0.141
2	−0.014	+0.143 +0.519
3	+0.073	+0.303
4	−0.038	−0.285 +0.141 +0.108
5	+0.067	+0.465

Case	Low Milk Fat	High Milk Fat
6	+0.137	−0.198
7	+0.038	−0.034
8	+0.043	−0.120
9	+0.037	−0.267

CHART II.—An aspect of the calcium metabolism in rickets. The favorable effect of cod liver oil on the calcium balance and the unfavorable effect of an abundance of milk-fat.

years ago a study of the effect of cod liver oil on negro children in a district of New York showed that it was of decided value in 80 per cent. of the cases. This test was carried out during the winter and early spring. Since this time, röentgen-ray examinations month by month in a series of cases have shown objectively the benefit of this therapeutic agent. It is quite remarkable how rapid is the deposition of calcium under this treatment.

It is possible to rid New York, or any locality, of rickets by

means of the use of cod liver oil. There are approximately 125,000 children in New York City between the ages of 3 and 15 months, the period of greatest susceptibility to rickets. If we estimate generously that the families of one third to one quarter of these children are unable to purchase cod liver oil, and if we agree that the development of rickets may be prevented by giving a teaspoonful three times a day, then, at the present cost, rickets could be practically abolished in this city by the expenditure of about $100,000 a year. This is merely one of many instances in which the community does not get the full benefit of our medical knowledge. A similar example exists in connection with the prevention of beriberi. As is well known, this disease is the main factor in the exceedingly high infant mortality in the Philippines, leading to a death rate in the city of Manila of 430 out of every thousand infants under 1 year of age. The preventive of beriberi is the water-soluble vitamin, which is furnished in high concentration in brewers' yeast, a by-product of the brewing industry. Yet this high mortality is allowed to continue unabated in spite of the fact that the country is under a stable, civilized government.

MALNUTRITION NOT TYPICAL DISEASE

The harmful effects of food deficiencies should not be associated in our minds, essentially or chiefly, with specific diseases such as scurvy or rickets, but rather as disorders of nutrition producing slight and manifold disturbances of function. This is probably quite as true of rachitic as of scorbutic malnutrition. It is probable that every organ or system in the body may be affected by faulty nutrition, so that the deficiency diseases must engage the attention of every physician, whatever his particular interest or specialty. For example, involvement of the eyes may lead to impaired vision or night-blindness; or, on the other hand, neuritis, cardiac enlargement, disturbances of the circulatory system, atrophic disorders of the skin, nails or hair, caries of the teeth, or unaccountable lack of appetite and constipation, may each in turn be the earliest symptom. A more careful inquiry into the dietary of patients will result in bringing to light

many cases in which vague and ill defined symptoms can be remedied simply by rendering the diet adequate.

The fat-soluble vitamin has been termed the "growth-vitamin." The designation is unfortunate, not only because this vitamin canot be credited with this specific faculty, but also because no single food constituent deserves such distinction, or is endowed with this all-important function. It is probably true that if the fat-soluble vitamin is deficient, growth will not progress normally. This is certainly the case with rats, which are particularly sensitive to a lack of this vitamin, but which require a very small amount to render their diet adequate. Similar observations have not, however, been made on infants, so that we do not know, even approximately, how much fat-soluble vitamin food is needed for normal growth. The stunting effect of a lack of antiscorbutic vitamin on infants has been definitely shown, so that with equal justice this might be termed the growth vitamin. The sounder physiologic view, however, would be to regard no food constituent as entitled to be styled the growth vitamin or factor. If an essential amino-acid, vitamin or inorganic salt is lacking in this dietary, this inadequate factor—whatever its chemical nature—must be regarded as and will prove to be the growth factor. In other words, for adequate growth the diet must be complete; and when it is incomplete—whatever the nature of the inadequacy, or however minimal its amount—growth will suffer.

INTERRELATIONSHIP OF NUTRITION AND INFECTION

Studies of the deficiency diseases have served to illustrate in a most convincing manner the intimate relationship of nutrition to infection, and have led our attributing increased significance to the former. Indeed, the chief clinical importance of disorders of nutrition seems to be associated with the fact that they bring about an abnormal condition of the tissues which renders them more susceptible to the invasion of bacteria or their products. This relationship was exemplified in 1913, when, as a result of a dietary of pasteurized milk, latent scurvy developed among a group of infants under our care. This "scorbutic taint" was

followed by a widespread grip infection, with hemorrhagic skin manifestations, which disappeared on the administration of orange juice. For some years I was uncertain how to interpret this peculiar clinical picture, whether to regard the epidemic as due to scurvy or to infection. As the result of subsequent experience I realized that it was due to both causes, the result of a primary nutritional disturbance and a secondary bacterial invasion. Another illustration of the interrelationship of disordered nutrition and infection is furnished by the frequent coincidence of nasal diphtheria and latent or subacute scurvy. This concurrence is so suggestive that when a large number of cases of nasal diphtheria develop, suspicion should be aroused that the infection was implanted on tisues rendered susceptible by scorbutic or other nutritional disorder. This view holds true for animals as well as for man. Veterinarians and farmers are well aware that faulty nutrition leads to fatal infections. The so-called "snuffles" of hogs is recognized as a disorder of this twofold nature. It is probable that plants which have been poorly nourished, owing to an inadequacy of the soil, also react by diminished resistance, and that this is a factor in the infectious diseases of plant life. This "nutritional-infectious" aspect has been convincingly illustrated on a large scale among the peoples of the Central Empires, who during the many years of the war suffered from various forms of malnutrition. The general impairment of health was most strikingly manifested both in adults and in children by the great spread of tuberculosis and its increased mortality. Davidsohn[15] has reported that in Berlin there was a marked increase in infection with tubercle bacilli in children under the age of 5 years, and that they had been infected earlier in life than formerly; whereas in 1913, 30 per cent. gave a positive reaction at 4½ years, in 1919 this percentage was reached at 2½ years. The mortality of children from tuberculosis showed a similar difference in the year previous to the war compared to that of the year succeeding the armistice, the figures being thirty-two as compared to about forty-eight deaths among children under 6 years of age, on the basis of 10,000 living individuals.

Clinical investigations in the domain of the deficiency diseases

have, as a rule, differed essentially from laboratory experiments. The latter, if accurately planned and correctly executed, study but one deficiency at a time; whereas the clinician investigating the dietary inadequacies of an individual or of a group, is necessarily confronted by a lack of more than one food factor. For example, an analysis of the cases of xerophthalmia or keratomalacia—a disorder ascribed to a lack of the fat-soluble vitamin —reported by Block of Copenhagen shows that many of the infants were receiving an insufficient quota not only of this vitamin but also of the antiscorbutic vitamin and of caloric food equivalents. Furthermore, in many localities where there was prolonged subnutrition during the recent war, there was a lack of vitamin, of adequate salts, of other essential substances and of calories. This confusion renders it impossible to unravel the clinical phenomena or to asign the various food factors their respective rôles. This criticism applies to the study of war or hunger edema which in 1917 spread through Poland and other countries, and which probably was the result of partial starvation combined with an unbalanced diet.[24] For this reason it is questionable whether we shall derive much increased knowledge from subsequent detailed reports concerning this vast experience of human suffering. On the other hand, a great deal will be learned in the future from clinical studies of nutrition when the diets are carefully controlled so that the results are capable of exact interpretation. We may expect such investigations to be undertaken more frequently and more intensively than heretofore.

On the other hand, for the laboratory worker there is the temptation to draw sweeping deductions from animal experiments, and to apply them *en masse* to the deficiency diseases of man. It should be remembered that the results of animal experiments are provisional and require the confirmation of clinical

[24] The experiences in the Central Empires during the war render it improbable that pellagra is due merely to a lack of adequate protein. Adequate protein was lacking to a marked degree—milk, cheese, eggs, meat were all unavailable. Nevertheless there was no prevalence of pellagra throughout these years.

experience. Only too often has it been found that laboratory conclusions which at the time seemed open to but one interpretation were later explained by unsuspected and entirely different factors. The pitfalls in dietary experiments on animals are especially numerous on account of the varying reactions of the different species, and because the artificial diet—in spite of the greatest care—may be incomplete in more than one particular. In vitamin experiments there is especial danger of attributing failure of growth and nutrition solely to a deficiency of this factor, on which the attention of the investigator is focussed, taking it for granted that the dietary is adequate beyond question in salts, protein and all other constituents. It is quite possible that this inconsistency will be found to invalidate some experiments that have seemed conclusive.

The disorders of nutrition have always presented a preeminent opportunity for collaboration between the laboratory and the clinic. It will be remembered that at one time the conception of rickets embraced a motley crew—congenital syphilis, scurvy, true rickets, achondroplasia and osteopsathyrosis, and that one by one these diseases were differentiated by the combined investigation of laboratory worker and clinician. The same opportunity exists today. The group of deficiency diseases furnishes urgent problems for the chemist, for the experimental biologist, the pathologic anatomist, the röentgenographer, and last, but above all, for the trained clinician. The subject is so complex that advance will be along various paths, each worker furthering and checking the work of the other, so that progress may not leap beyond the bounds of well-founded experimental or clinical evidence.

NATIONAL CHANGES IN HEALTH AND LONGEVITY

By SIR ARTHUR NEWSHOLME, K.C.B., M.D.*

Resident Lecturer in Charge of Public Health Administration, School of Hygiene and Public Health, Johns Hopkins University.

THE subject roughly indicated in the title as announced, evidently cannot be even outlined in an hour's address; and my remarks will deal chiefly with some of the changes in longevity in England, and, so far as they are ascertainable, in this country. After a more general introduction, I propose to confine my review to men, merely indicating now that improvements in the male have in nearly every instance been exceeded in the female. As will be seen shortly, I propose furthermore, to limit my comparisons chiefly to the period beyond the 40th year of human life.

The object of Preventive Medicine may be stated to be to secure long life with enhanced health. The mere desire for long life may, from a certain angle, be regarded as including some ignoble elements. There is a sense which we must agree with the Wisdom of Solomon:

"Honorable age is not that which standeth in length of time, nor is measured by number of years. He being made perfect in a short time fulfilled a long time"

(Apocrypha, Wisdom of Solomon, Chap. IV. Verses 8 and 13.)

Although it is the desire of every man to die of old age, there are many passions more powerful. As Lord Bacon said—

"There is no passion in the mind of man so weak, but it mates and masters the fear of death....Revenge triumphs over death; love slights it; honor aspires to it; grief flyeth to it; fear pre-occupateth it."

But to die of old age is the laudable ambition of all.

We may assume that death is a normal, though the last,

* Delivered January 29, 1921.

act of life. In Goethe's words, "Life is the most exquisite invention of Nature, and death is her expert contrivance to get plenty of life."

To die of age is comparatively rare. Disease and accident, in times of peace, are the chief causes of death in civilized communities; and premature and therefore wasteful death is

AGE AT WHICH POPULATION IS REDUCED TO ONE-HALF POPULATION AT BIRTH
(Life-Table Experience)

	Experience of	Males	Females
England and Wales	(1901-10)	58-59 years	62-63 years
England and Wales	(1909-11)	61-62 years	65-66 years
United States of America			
Experience of	(1909-11)		
Entire Population	Original Registration States	58-59 years	62-63 years
White	Original Registration States	59-60 years	63-64 years
Negro	Original Registration States	34-35 years	40-41 years
Native White	Original Registration States	60-61 years	64-65 years
White in Cities	Original Registration States	55-56 years	60-61 years
White, rural	Original Registration States	65-66 years	67-68 years
Indiana		64-65 years	66-67 years
Massachusetts		58-59 years	62-63 years
Michigan		64-65 years	66-67 years
New Jersey		57-58 years	62-63 years
New York		55-56 years	61-62 years

the rule among us. This is illustrated by the following table, showing in various life-table experiences the age at which a given number (say 100,000) starting at birth become reduced to half their original number (say 50,000).

(It is convenient here to explain for the benefit of non-technical readers that a life-table represents "a generation of individuals passing through time." Theoretically it may be formed by actually watching a large group of persons from birth to death, and ascertaining the number of

survivors and the average future expectation of life at each successive birth-day. But such a life-table would be obsolete before it could be utilized; and in the life-table figures quoted hereafter, the death-rates for each age-period of life during a short series of years are assumed to determine the number of survivors to the next age-period, who are then subject to the death-rate of the next age-period in the same years, and so on.)

Dr. Farr (35th Ann. Rep. of Reg. General) described the age between 45 and 55 as the middle arch of life, as shortly after the age of 45 was reached, a million born at the same time were reduced to half a million. Now a much larger proportion past this middle arch of life.

In most of the above communities half of the total population born has scarcely disappeared before reaching the 60th annual turnstile.

This is true for a life-table population in which a given number of persons are traced through life on a fixed basis of experience. In actual life, there is in most communities a greater stream of incoming new lives by birth than of departing lives; and the loss of life under these circumstances is heaviest in the earlier years of life. This is illustrated in the following table giving the proportion of deaths at all ages which occurred at different age-periods in

ENGLAND AND WALES, 1901-10

PROPORTION OF DEATHS AT ALL AGES (=100) OCCURRING AT DIFFERENT AGE-PERIODS.

Age	Males		Females	
First 5 years	35.0		31.0	
Twenty years 5-25	7.8		8.3	
Twenty years 25-45	12.6		12.2	
Twenty years 45-65	20.8)	44.6	19.1)	48.5
Ages 65 and upwards	23.8)		29.4)	
	100.0		100.0	

Thus in actual experience only 44.6 per cent of the male and 48.5 per cent of the female deaths occur at ages over 45.

THE VITAL SUPERIORITY OF THE FEMALE

It will be noted that a smaller proportion of female than of male deaths occur in early life; also that on the average females live longer than males; and the following table shows that at every age except between 5 and 15, the female is lower than the male death-rate at corresponding ages.

PERCENTAGE EXCESS OF MALE OVER FEMALE DEATH-RATE AT EACH AGE-PERIOD DURING TWO DECENNIA.*

EXPERIENCE OF ENGLAND AND WALES

Age	1851-60	1901-10
0	+15	+19
5	+ 1	— 3
10	— 3	— 5
15	— 9	+ 7
20	+ 4	+19
25	— 4	+17
35	+ 3	+22
45	+18	+30
55	+14	+28
65	+11	+20
75 and upwards	+ 6	+12

The death-rate at every age in both sexes has declined; but males show an increasing excess of mortality as compared with females, amounting to a maximum excess of 30% at the age-period of 45-55. The excess of female over male mortality at ages 5-15 in 1901-10 and at ages 10-15 in seven consecutive decennial periods of English experience would form an admirable subject for further study. Excepting at these ages the superiority of female over male vitality is evident throughout life; a fact which is perhaps too little known.

In England and Wales, for every 1,000 live births of female infants there were 1049 live births of male infants in 1841-50,

*This and most other tables given in this paper are derived from Dr. Stevenson's contributions to the Reports of the Registrar General of England and Wales.

the proportion slowly falling to 1038 in 1901-10, and rising again to 1045 to every 1000 female births in the three years 1916-18.

In the birth registration area of the United States in 1918 the proportion of male to female live births was 1059 to 1000 among the white and 1020 to 1000 among the negro population.

But this excess of male over female is soon removed. The superiority of the female in the struggle for survival is shown markedly in the first day after live-birth, through every week of the first month, and in each trimester of the first year of

DEATH-RATE PER 1000 BIRTHS AT EACH PERIOD OF INFANCY

	England and Wales. 1918		United States-Birth Registration Area. 1918.	
	Males	Females	Males	Females
Under one day	12.6	9.6	17.6	13.1
1 day and under 1 week)	13.3	10.7	17.0	13.1
2nd week	6.0	4.9	6.5	5.4
3rd week	5.2	3.8	4.8	3.9
4th week	3.9	2.8	3.7	3.1
Total under 1 month	41.0	31.8	49.6	38.6
1 to 3 months	18.9	15.0	17.1	13.7
3 to 6 months	18.1	13.6	17.9	14.5
6 to 9 months	15.6	12.6	14.5	12.7
9 to 12 months	14.3	13.0	11.7	11.1
	107.9	86.0	110.8	90.6

extra-uterine life; and is shown in American and English experience alike. By the end of the second year of extra-uterine life girls number more than boys. That greater facility of birth of females owing to a smaller cranium is not the sole cause is evidenced by the persistence of the phenomenon of superior vitality.

DEATH-RATES AT DIFFERENT AGES—INCREASES AND DECREASES

For the registration area of the United States comparisons are

only possible between 1900 and subsequent years. In the following table the American experiences for the single years 1900 and 1911 are quoted from the Mortality Statistics, 1911 (Bureau of Census) page 22. The death-rates for the same years and ages are given for England and Wales.

MALES—DEATH-RATE PER 1000 LIVING AT EACH AGE.

Year	0—	5—	10—	15—	20—	25—	35—	45—	55—	65—	75 and over
1900 (England and Wales	61.6	4.2	2.3	3.7	5.1	6.7	11.7	19.9	37.1	74.2	168.3
1900 (U.S.A. Reg. Area ..	54.2	4.7	2.9	4.9	7.0	8.3	10.8	15.8	28.9	59.6	146.1
1911 (England and Wales	46.2	3.5	2.0	3.0	3.9	5.0	8.0	14.8	29.7	63.5	150.4
1911 (U.S.A. Reg. Area ..	39.8	3.4	2.4	3.7	5.3	6.7	10.4	16.1	30.9	61.6	147.4

The differences are interesting, but it will be desirable to compare the experience of other years before final conclusions are drawn. In 1900, at ages 0-5 and at all ages over 35, registration America had a more favorable male death-rate than England; in 1911 its superiority at higher ages was confined to ages over 65. In 1900 the English death-rate at ages 0-5 was 14 per cent and in 1911 was 16 per cent higher than that of America (registration area). Evidently then, in view of the higher infant mortality in America, the death-rate at ages over 1 and under 5 is lower in the States than England, a subject worthy of further study. For all ages the standardized death-rates of England and Wales was 19.9 per 1000 population in 1900 and 15.6 in 1911; of the original registration area of the U. S. A. 17.6 in 1900 and 15.3 in 1911; there being a 22% improvement in England, and a 13% improvement in the registration area.

THE INCIDENCE OF REDUCED DEATH-RATE AT DIFFERENT AGES

In the next table the historical trend is shown of the death-rates of England and Wales in five decennial periods, the increase or decrease of the death-rate for various age groups being displayed. The table also shows a similar comparison between the experience of 1911 and 1900 for the registration area of the United States.

It will be noted that the American experience displays for the later period an increased death-rate in men at all ages over 45, and in women at ages 55 to 75.

When the experience of 1871-80 is contrasted with that of 1861-70, the English experience shows an increased death-rate at all ages over 35 for males, and at ages over 55 for females. When 1881-90 is contrasted with 1871-80 there is no evidence of increased death-rate at any age except in men aged 65-75; and the experience of the 20 years 1891 to 1910 show a declining death-rate in both sexes at all ages, with the exception of a slight increase at ages 55-65 in males and at ages 65-75 in females in 1891-1900, due probably to the influenza pandemic of 1889-93. The evidence is definite that there has been steady advance in the age to which increasingly favorable death-rates extend.

Thus a comparison of the experience of (the death registration area of) the United States with that of England and Wales shows that the registration area stands historically in respect to increase or decrease of death-rate at various stages of life approximately where England stood in 1871-80; and it is not very hazardous to make the same forecast for it, as I ventured to make for England in the year 1893, when the first "Brighton Life-Table" was prepared by me.*

In that publication, I pointed out that—

"It is evident that although in England, owing to the large number of lives saved during the early years of life, the number surviving to the higher ages has increased, thus securing a great gain to the community, this is not incompatible with a stationary or even diminished prospect of

* (See also P. 316 of the author's "Elements of Vital Statistics," 1899)

life for each individual over a certain age. In England the death-rate for males was higher in 1871-80 for *all age-groups above the 25-35 period,*

INCREASE OR DECREASE PER CENT OF THE MORTALITY IN EACH SEX AND AGE-GROUP COMPARED WITH THE MORTALITY IN THE SAME GROUP IN THE IMMEDIATELY PRECEDING DECENNIUM.

	England and Wales				Death Registration Area. U.S.A.
	1871-80 compared with 1861-70	1881-90 compared with 1871-80	1891-1900 compared with 1881-90	1901-10 compared with 1891-1900	1911 compared with 1900
			Males		
Under 5	— 6.9	—10.0	+ 1.8	—20.2	—26.6
5	—18.1	—20.3	—19.4	—18.7	—27.7
10	—17.3	—20.4	—17.1	—16.1	—17.2
15	—15.1	—17.8	—12.2	—18.5	—24.5
20	—13.1	—22.1	—11.7	—17.4	—24.3
25	— 6.0	—16.9	—13.0	—17.6	—19.3
35	+ 2.3	—10.2	— 7.2	—20.4	— 3.7
45	+ 4.2	— 3.5	— 2.2	—14.4	+ 1.9
55	+ 5.2	— 0.5	+ 0.7	— 9.0	+ 6.9
65	+ 3.9	+ 1.1	— 0.1	— 7.9	+ 3.4
75 and over	+ 2.3	— 3.9	— 1.6	— 4.8	+ 0.9
			Females		
Under 5	— 8.4	—11.0	1.6	—20.7	—27.3
5	—20.1	—15.6	—16.9	—17.3	—32.6
10	—17.5	—16.4	—17.5	—15.6	—32.3
15	—17.9	—18.9	—17.1	—21.1	—31.3
20	—14.6	—18.7	—19.5	—21.6	—29.9
25	—11.4	—14.4	—17.5	—22.0	—26.8
35	— 3.6	— 9.0	— 9.4	—21.5	—15.3
45	— 0.2	— 3.3	— 2.4	—15.1	— 9.2
55	+ 2.7	— 0.7	— 0.1	—12.6	+ 0.8
65	+ 3.2	— 1.0	+ 0.5	—11.2	+ 2.4
75 and over	+ 0.8	— 5.2	— 1.1	— 7.0	— 0.2

and for females was higher in 1871-80 for all age-groups above the *35-45* period than in preceding decennial periods."

After discussing the influence of increased wages and improved nutrition in more than counterbalancing the unfavorable influence of city conditions of life, I laid stress on the following

factor which must, I believe, be credited with a large share of the credit for the reduced death-rate at older as well as at younger ages which has now been realized.

"Another consideration requires to be borne in mind. We are at present in a transition period. The Public Health Acts of 1871 and 1875 heralded immense improvements in sanitation, the fruits of which have not yet been fully reaped. There has been, more especially since 1875, steady and increasing improvements in the conditions under which people live. Men now 40 years of age were born in the pre-sanitary period; and the first 20 years of their life were spent under more unhygienic conditions than those now holding good. This fact would go far towards explaining a stationary death-rate at the higher ages. It does not, however, explain an increased death-rate at those ages."

"The explanation of this increased death-rate at the higher ages will probably be evident, when at the end of another 20 or 30 years the improved conditions of life have endured sufficiently long to enable their full force and value to be determined. We must be content in the meantime to have stated the more important factors which appear to be at work, leaving the complete solution of the problem to a time when the statistical experience of our country is more mature."

At the end of the time asked for in the above comment, it is noteworthy that at every age, even beyond 75 years of age, the number dying from a given number at risk has decreased; and the improved conditions of modern life, sanitary, social, and economic, have resulted in England in a lowered death-rate at every recorded age-period.

It is unfortunate that a similar comparison can be made for the registration area of the United States only for 1900 and 1911; which, as already stated, displays a difference similar to the one displayed when the English death-rates at different ages in 1871-80 are compared with corresponding death-rates for 1861-70.**

** The above statement gives the historical position. It will be noted, however, that the standardized total American death-rate in 1911 was 15.3 as compared with 15.6 for England and Wales.

I am able to give the following additional contribution to the historical position. In the annual report of the Massachusetts Board of Health for 1896 is given a comparison of the death-rate according to age for *both* sexes in combination in 1875 and 1895 respectively.

Death-rate, Massachusetts, U.S.A.

	0	5	10	15	20	30	40	50	60	70	80
1875	73.9	9.8	4.7	7.7	10.5	11.3	13.0	18.3	34.8	71.1	176.4
1895	64.5	6.2	3.2	5.3	7.1	9.7	12.7	20.5	39.4	82.4	184.7

It will be noted that the death-rate had increased between 1875 and 1895 at each age period after 50. A somewhat similar increase has occurred between 1900 and 1911.

CHANGES IN ADULT MORTALITY

Having given a brief outline of the general lowering of the death-rate in both sexes at all ages, with the exception of a slight share of women in this improvement, I propose now to confine my observations to the historical changes after the age 25, and more particularly to events after the 40th milestone of life has been passed; as it is especially concerning this period of life that our professional pessimists,—as always in the past,—insist that we are "going to the dogs."

It is particularly unfortunate that these historical comparisons, owing to the absence of comparable American data, must be limited chiefly to English experience with a relatively stable population and long experience of accurate vital statistics.

For England and Wales as a whole, a consecutive series of life-tables enables comparisons to be made for long series of years. In the following tables, the facts are shown for males.

Table A. shows that in each successive life-table the number of survivors to the age of 25 out of equal numbers born has continuously increased with lapse of time.

The subsequent course of events for adult life can more accurately be followed in Table B. It will be seen that with the exception of ages 60 and upwards in the decennium 1881-90, the number of survivors out of every 1000 reaching the age of 25 years has steadily increased until after the Psalmist's term of life is passed.

Similarly, out of every 1000 reaching 40 years of age, with the exception of ages 55 and upwards, in 1881-90, improvement in expectation of life is shown at all ages over 40.

These tables give no evidence of national deterioration at

ENGLAND AND WALES LIFE-TABLES—MALES Massachusetts, U.S.A. Males

("In the following tables, the facts are shown for males".)

A.

Number of Survivors at Higher Ages, out of 1000 Born.

Experience of	1838-54	1881-90	1901-10	1910-12	1893-97	1909-11
No. at Birth	1000	1000	1000	1000	1000	1000
No. at Age 25	624	694	745	779	680	760
30	595	669	727	762	651	739
35	564	640	705	742	620	713
40	532	605	677	717	588	683
45	496	564	642	685	554	646
50	456	518	599	643	515	604
55	409	463	544	590	468	551
60	356	398	476	521	411	482
65	295	322	393	435	344	395
70	223	239	299	334	267	296
75	148	154	198	224	185	197

B.

Number of Survivors at Higher Ages, out of 1000 at Age 25.

25	1000	1000	1000	1000	1000	1000
30	954	964	976	978	958	972
35	904	922	946	952	912	938
40	852	872	909	920	865	899
45	794	813	862	879	815	850
50	731	746	804	826	758	795
55	655	667	730	758	688	725
60	570	574	639	669	604	634
65	473	464	528	558	506	520
70	357	344	401	429	393	389
75	237	222	266	288	272	259

C.

Number of Survivors at Higher Ages, out of 1000 at Age 40.

40	1000	1000	1000	1000	1000	1000
45	932	932	948	956	942	946
50	857	856	885	897	876	884
55	769	765	804	823	796	807
60	669	658	703	727	699	706
65	556	532	580	606	585	578
70	420	395	442	466	454	433
75	278	255	291	312	315	288

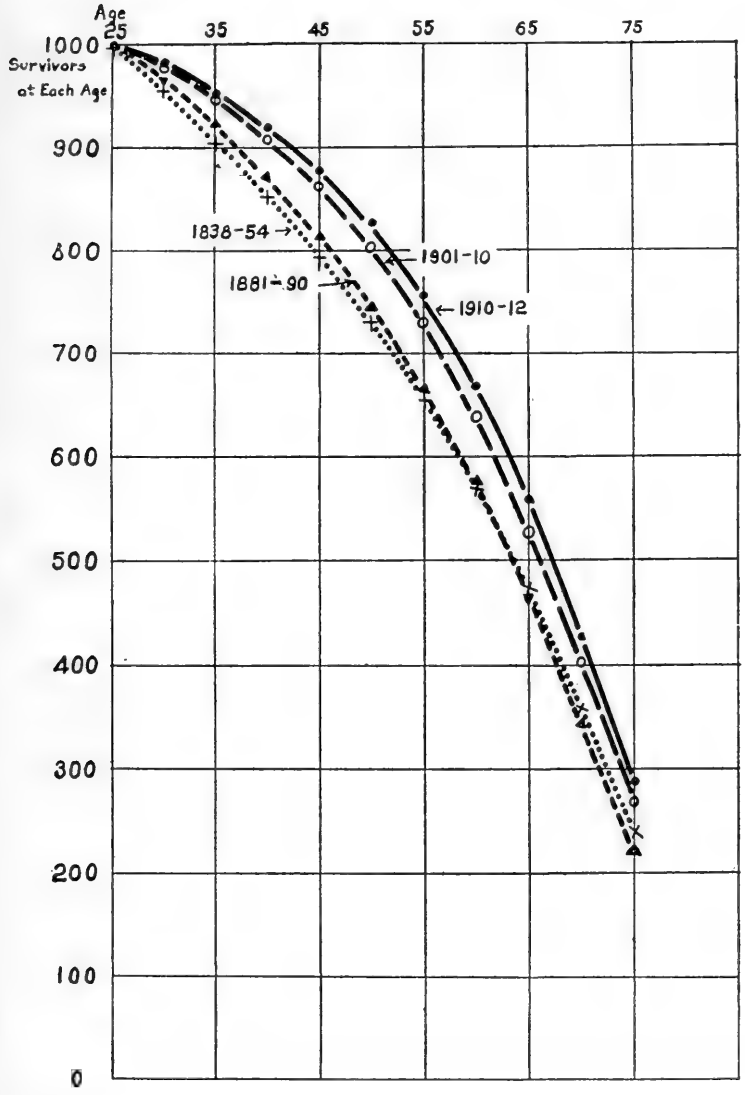

FIG. I.—LIFE TABLE EXPERIENCE, ENGLAND AND WALES, FOR FOUR PERIODS. Number of male survivors at each subsequent age out of 1,000 at age 25, in 1838-54, 1881-90, 1901-10 and 1910-12.

United States Life-tables, 1909-11.—Males

A.

Number of Survivors at Higher Ages, out of 1000 Born.

	Total White Males (Rural Parts)*	Native Born White Males*	Total White Males*	White Males in Cities*	Indiana	Michigan	New Jersey	New York	Massachusetts
No. At Birth ..	1000	1000	1000	1000	1000	1000	1000	1000	1000
No. At Age 25..	806	768	770	751	804	791	764	756	760
30..	785	744	748	728	782	771	741	731	739
35..	763	716	721	698	757	749	712	701	713
40..	738	683	688	662	732	725	677	662	683
45..	710	648	651	619	702	698	637	619	646
50..	677	608	607	569	667	663	591	569	604
55..	637	561	556	510	628	621	537	511	551
60..	581	501	490	435	570	565	466	440	482
65..	506	426	409	347	498	489	381	358	395
70..	409	337	315	253	404	393	288	269	296
75..	294	237	216	162	290	279	194	180	197

B.

Number of Survivors at Higher Ages, out of 1000 at Age 25.

25..	1000	1000	1000	1000	1000	1000	1000	1000	1000
30..	974	969	971	969	973	975	970	967	972
35..	946	932	936	929	942	947	932	927	938
40..	916	889	894	882	911	917	886	876	899
45..	881	844	846	824	873	882	834	819	850
50..	840	792	788	758	830	838	774	753	795
55..	790	731	722	679	781	785	703	676	725
60..	721	652	636	579	709	714	610	582	534
65..	628	555	531	462	619	618	499	474	520
70..	507	439	409	337	503	497	377	356	389
75..	365	308	280	216	361	353	254	238	259

C.

Number of Survivors at Higher Ages, out of 1000 at Age 40.

40..	1000	1000	1000	1000	1000	1000	1000	1000	1000
45..	962	949	946	935	959	963	941	934	946
50..	917	890	882	860	911	915	873	859	884
55..	863	821	808	770	858	857	793	772	807
60..	787	734	712	657	779	779	688	664	706
65..	686	624	559	524	680	675	563	540	578
70..	554	493	458	382	552	542	426	406	433
75..	398	347	314	245	396	385	287	272	288

*In the Original Registration States.

higher ages. They show, on the contrary, increased longevity in each succeeding period.

This is further illustrated in Fig. 1.

For the United States death registration area* historical comparisons are only practicable for 1900 onwards, except for Massachusetts, for which Dr. S. W. Abbott, the Secretary of the then State Board of Health constructed a life-table based on the experience of the years 1893-97,† the data for which are probably comparable with those for Massachusetts published in the life-table volume of the Federal Census Bureau. In this volume is given *inter alia* a life-table for Massachusetts, based on the experience of 1909-11; and in the table these two experiences are compared.

The results when the whole of life is taken into account show improved prospects of life in every age period in Massachusetts; so in the main do the figures for equal numbers starting at age 25; but for equal numbers starting at age 40, there appears to be slight vital deterioration from age 65 and upwards.

Although the materials for historical comparisons in U. S. A. are scanty, the series of life-tables issued by the Bureau of Census, based on the deaths in the 3 years 1909-11 and the population of 1910, give valuable material for comparison with the data for England and Wales. Dr. Wm. H. Davis, the Chief Statistician for Vital Statistics of the Census Bureau, informs me that the English and American life-tables are comparable, in respect of methods of construction. In the following table are compared the number of survivors out of 1000 males at birth, at age 25, and in each successive five additional years of age. The columns are arranged in order of the number of survivors to the highest age, beginning with the experience of greatest vitality.

It will be noted that the aggregate white males in the rural parts, and in the whole of the registration area, and the pop-

* This area comprised in 1900, 40.5% of the total population of the U.S.A.

† The 30th Annual Report of the State Board of Health of Massachusetts for 1898 gives also an earlier life-table for persons in Massachusetts dealing with the experience of the year 1855.

ulation of the States of Indiana and Michigan showed the largest number of survivors to age 25, Michigan coming next.‡

If the experiences from age 25 onwards be compared, rural males, the males of Michigan and of Indiana have approximately an equal number of survivors to the age 70, while Massachusetts, New Jersey, and New York States have relatively few.

The following table compares the experience of males in England and Wales in 1910-12, with that of white males and white native-born males in the registration area of the United States in 1909-11.

In Figure 2. the relative experience of urban and rural populations and of Massachusetts is shown.

The picture is not materially changed when the survivorship of 1000 men starting at age 40 in each of these states is contrasted. The populations living preponderantly in cities evidently occupy an inferior position. That the conditions of city life explain, largely at least, the marked differences of vitality in the different states is suggested by the partial coincidence between the degree of urbanization and the paucity of survivors. At the census of 1910, 92.9% of the population of Massachusetts was urban (i.e. lived in districts with population exceeding 2500); 78.9% in New York; 75.2% in New Jersey, as against 47.2% in Michigan and 42.5% in Indiana. The proportion of foreign born population in 1910 was about 32% in Massachusetts and New York State; 29.5% in New Jersey; 22.1% in Michigan, and 9.2% in Indiana. It may be added that for every 100 foreign born persons in Massachusetts the highest proportion is Irish (21.2%), in New York, Russians (20.5%), Italians (17.3%), and Germans (16.0%) coming next.

SUMMARY

The close similarity between the experience of the male population in adult life in England and in the United States is striking. It is, further, noteworthy that the inclusion of

‡ Separate life-tables have been published for Indiana, Massachusetts, Michigan, New Jersey and New York.

A.

Number of Survivors at higher ages out of 1000 Born.

* Original Registration States	England and Wales	United States.* 1909-11	
	Males 1910-12	All Native-born White Males	All White Males
No. at Birth	1000	1000	1000
At Age 25	779	768	771
30	762	744	748
35	742	716	721
40	717	683	688
45	658	648	651
50	643	608	607
55	590	561	556
60	521	501	490
65	435	426	409
70	334	337	315

B.

Number of Survivors at higher ages out of 1000 at Age 25.

At Age 25	1000	1000	1000
30	978	969	971
35	952	932	936
40	920	889	894
45	879	844	846
50	826	792	788
55	758	731	722
60	669	652	636
65	558	555	531
70	429	439	409
75	288	308	280

C.

Number of Survivors at higher ages out of 1000 at Age 40.

At Age 40	1000	1000	1000
45	956	949	946
50	897	890	882
55	823	821	808
60	727	734	712
65	606	624	595
70	466	493	458
75	312	347	314

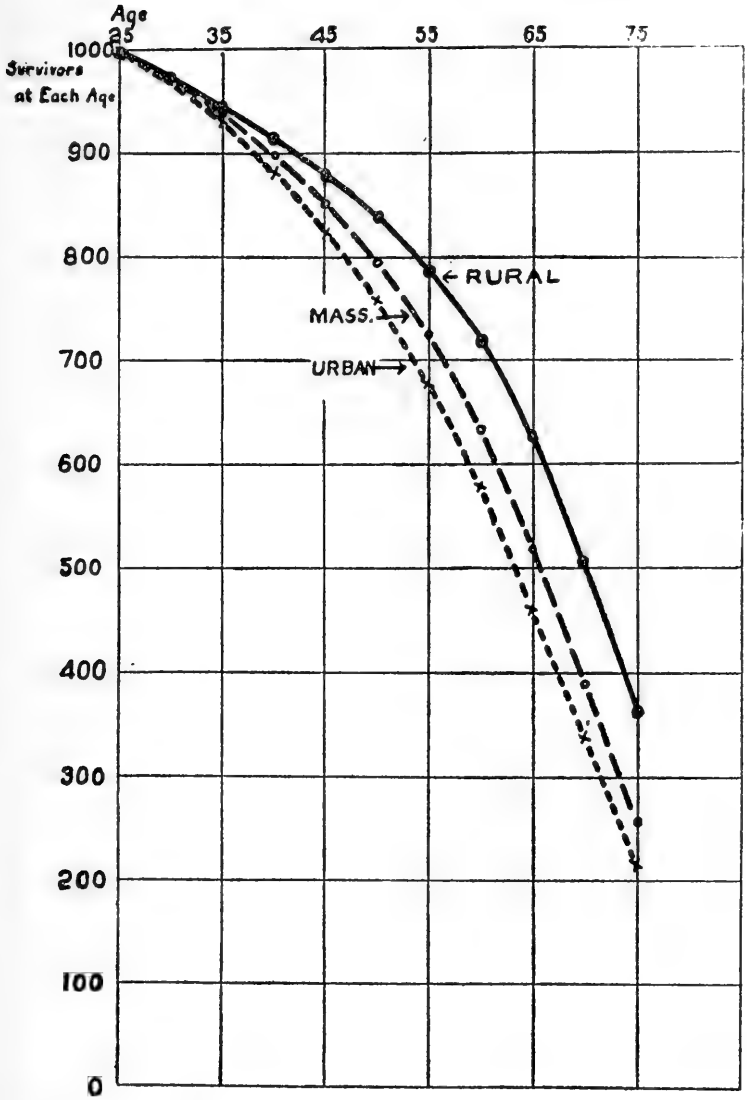

FIG. II.—LIFE TABLE EXPERIENCE OF THE UNITED STATES (1909-11). Number of male survivors at each subsequent age out of 1,000 at age 25 in the aggregate urban and rural white populations of the original registration states and in Massachusetts.

foreign with native whites does not result in a very marked change in survivorship at the higher ages.

Summing up the teaching of the preceding tables we arrive at the following conclusions:—

1. The vital experiences of England and Wales and of the death registration area of the United States are very similar, and almost equal.

2. At nearly all ages, including the first year of life, females have an intenser inherent power of survival than males; and females have profited more than males from the increased vitality at all ages in recent years.

3. English experience shows in successive decennial periods a reduction of death-rate which encroaches on the higher ages with advance of time. After the end of the decennium 1881-90, with a magnificent exception, each age up to the end of life has shared in the reduced rate of mortality.

4. Stated in terms of survivorship, out of every 1000 reaching 40 years of age, improvement in expectation of life (depending on the summation of survivors at all higher ages) is shown at all ages over 40, with the exception of ages over 55 in 1881-90.

5. This temporarily increased death-rate at higher ages, which was probably associated with the Influenza Epidemic of 1889-93, has been followed by a marked decline of death-rate at these higher ages.

6. The satisfactory result is shown in English experience of a diminishing death-rate at all ages, though on a much greater scale in the younger than in the more advanced years of life.

7. A comparison of the life-table experience of Massachusetts at an interval of twelve to fifteen years gives no evidence of vital improvement.

8. The current life-table experience of the white population of the United States (registration area) is almost identical with that of England; the male population (whites) of both countries have an almost equal chance of survival to the age 25; and for equal numbers starting at the age of 25 or at the age 40, the native born white population of America have a larger pro-

portion of survivors to the age 75 than the population of England.

9. The position of the negro is lamentable, assuming that in the registration area of the States, the figures are trustworthy.**

10. For the rural parts of the population the expectation of life and the number of survivors to age 75 are much higher than in the entire registration area, while in cities and in the three States—New Jersey, New York and Massachusetts,—having a preponderantly city population,—life is considerably curtailed.

INCREASE IN TOTAL DEATH-RATE IN U. S. A. AT AGES OVER 45.

Three facts emerge prominently from the above study of the American and English vital statistics: 1st, that in England there has for several decades been an almost continuous fall in the total death-rate, affecting middle and advanced as well as early life; 2nd, that the average position of the white population of the United States (registration area) and that of England are approximately equal; although 3rd, it appears that the male death-rate at ages over 45 in the United States is still slightly increasing beyond what it was 11 years earlier. Why is this?

An explanation has already been suggested, if it be admitted that time is needed for the results of almost inseparable social and sanitary improvements to be felt at all ages. Her vital

** 1000 male negroes are reduced to one-half between their 34th and 35th birthday, while this does not happen for the white population before the 59th birthday is reached.

** I doubt whether this figure can be trusted. Deficient birth registration among the negroes may have vitiated to some extent the life-table estimates of negro population at ages 0-5, and increased the apparent death-rates during this period. This would not, however, influence the number of survivors in a life-table population out of 1000 males who reach the age 25 as shown in the following table:—

	Age										
Total White Pop.)	25	30	35	40	45	50	55	60	65	70	75
Reg. Area U.S.A.)	1000	971	936	894	846	788	722	636	531	409	280
Negroes)											
Reg. Area.)	1000	938	865	787	704	614	516	413	309	213	130

position is equal to that of England, due possibly to the higher wages, better nutrition and less alcoholism, of the mass of the American as compared with the mass of the English population. And yet she is still historically in the position as to age distribution of death-rates occupied by England in 1871-80, when the older portion of the English population had not enjoyed in their childhood the social-sanitary betterment which their children enjoyed. This being so, we may anticipate an extension of the reduced death-rate in the United States at all ages ere long.

This view as to the reason for the failure of the American population at the higher ages to share in the reduced death-rates of earlier life, is confirmed by the complex position of this country with respect to immigration. As already seen, nearly one-third of the population of the States of Massachusetts, New York and New Jersey are foreign-born, and of the remaining two-thirds about half have foreign parentage, or mixed foreign and native parentage. These foreigners are derived in varying proportions from Germany, Ireland, Italy, Russia and Austria-Hungary, in some of which countries they have in earlier life been permanently exposed to circumstances of malnutrition and insanitation; and they, furthermore, in their earlier years residence in the States have been subjected possibly to excessive strain and privation, in circumstances of insanitation. It would be surprising if there were not a persistently high or even an increased death-rate of persons at higher ages in the registration area. This subject has been elucidated statistically by Dr. Louis I. Dublin, who has shown that the foreign-born in New York and Pennsylvania experience a higher death-rate than native born of native parentage at nearly all older ages, and that this holds good also for native born of foreign or mixed parentage.**

THE REGISTERED INCREASED MORTALITY FROM SPECIAL DISEASES

Having arrived thus far, we are now able to consider the statements frequently made as to special causes of alleged in-

** The Mortality of Race Stocks in Pennsylvania and New York, by L. I. Dublin and G. W. Baker (Amer. Publ. of the Amer. Statist. Assoc. March, 1920)

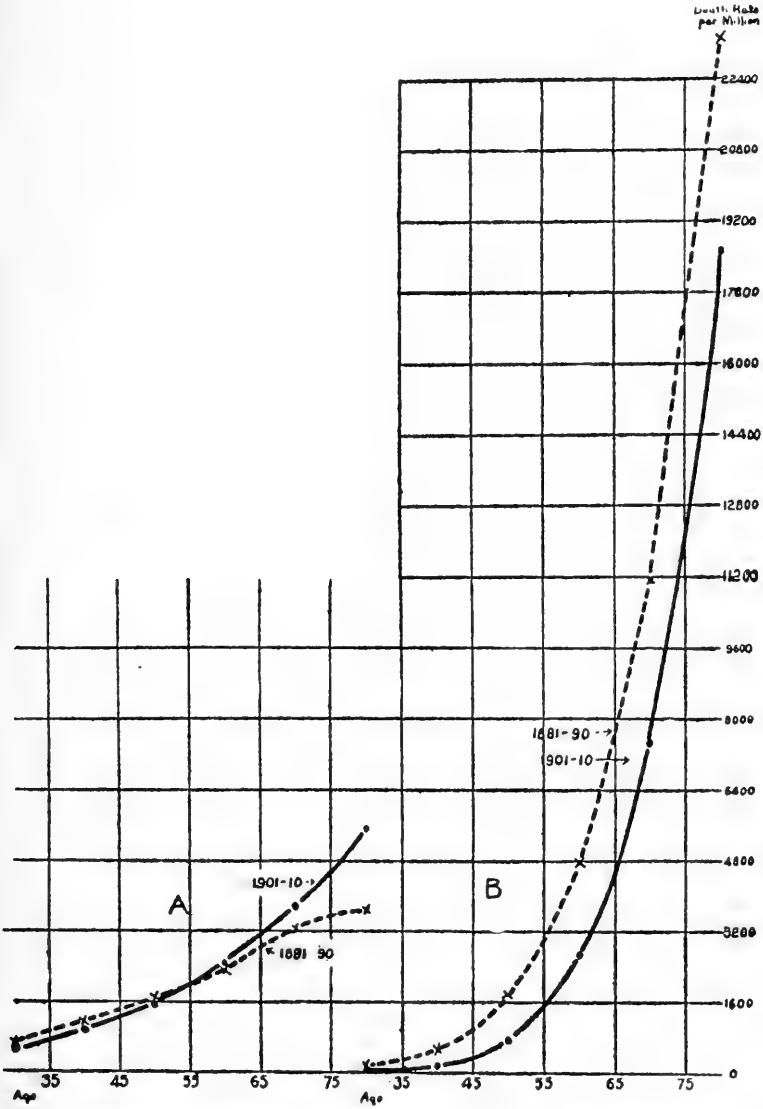

FIG. III.—DEATH RATE PER MILLION MALES AT EACH AGE PERIOD IN 1881-90 AND 1901-10 from

A. Pneumonia. B. Bronchitis.

creased mortality at higher ages. The following statement, based doubtless on official published figures, may be quoted as typical of numerous statements to a similar effect, published in scientific journals and in the daily press.

"The death-rate from degenerative diseases in the U. S. registration area has increased 41% in 20 years. By this term is meant the wear-and-tear diseases such as cancer, arterio-sclerosis, Bright's disease, etc., which are due to bad personal habits."

In examining the question as to whether this increase is real or apparent, or only partially real, we need to remember the limitations of accuracy of medical certification of death. There has been steady improvement in medical certification, but this in itself has necessitated caution in accepting historical comparisons of diseases. The rule of safety in making historical comparisons is to confine such comparisons to individual diseases, and not combine them into groups, as "circulatory," "renal," "nervous," and so on. The same rule applies, though to a less extent, when making contemporaneous comparisons. If I depart from this council of wisdom in what follows, it is to illustrate the dubiety attaching to the statistics thus displayed.

PNEUMONIA AND BRONCHITIS

Even for diseases like pneumonia and bronchitis, there is some ambiguity in historical comparisons of statistics. There is not only change in medical fashions of certification, but also in one period a larger share of pneumonia may be secondary to uncertified influenza, or of bronchitis or pneumonia to uncertified measles, than in another period. In the following curves the death-rates from pneumonia and bronchitis, respectively, in England and Wales among males at various ages over 25 for the two periods 1881-1890 and 1901-10, respectively, are compared.

The decline in the male death-rate from bronchitis at each age-group is noteworthy; as is also the fact that in the decennium 1901-10 the death-rate from pneumonia increased only

at ages 65 and upwards. Notwithstanding the increased longevity of the population, in the year 1918, in England and Wales, only 3.8% of the total male deaths was attributed to "old age," or "senile decay," while in the 25 years, 1848-72 in-

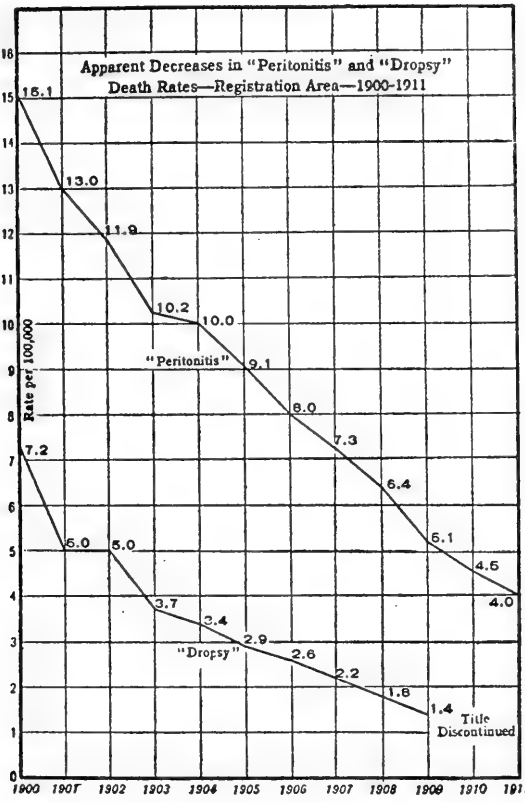

FIG. IV.—ILLUSTRATING TRANSFERENCE OF CAUSES OF DEATH.

clusive, the number under this heading averaged 5.1% of the total deaths. Even more striking as illustrating changes in the medical certification is the following illustration of American experience, borrowed from a paper by Dr. L. I. Dublin on "The Registration of Vital Statistics and Good Business."

CARDIAC AND RENAL DISEASES

These considerations apply with even greater force when historical comparisons are made of the mortality from cardiac and renal diseases, as shown for the English experiences in 1881-90

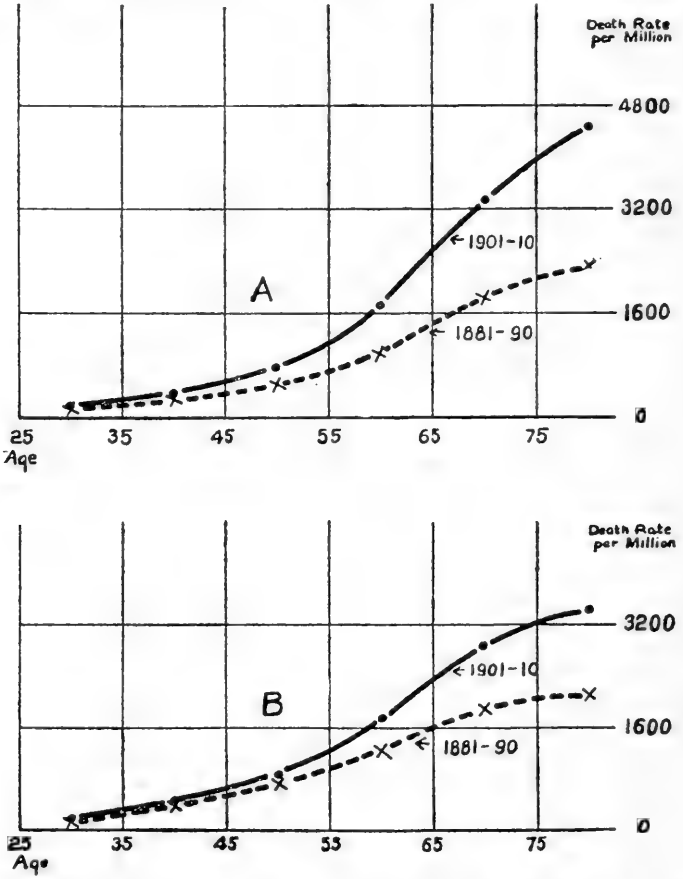

FIG. V.—DEATH RATE PER MILLION MALES AT EACH AGE PERIOD OVER 25 IN 1881-90 AND 1901-10
A.—Valvular disease of the heart, endocarditis angina pectoris.
B.—Acute and chronic nephritis, Bright's disease.

and 1901-10 respectively. After the age 45, an increase is shown in the death-rate (stated in terms of the population at the ages

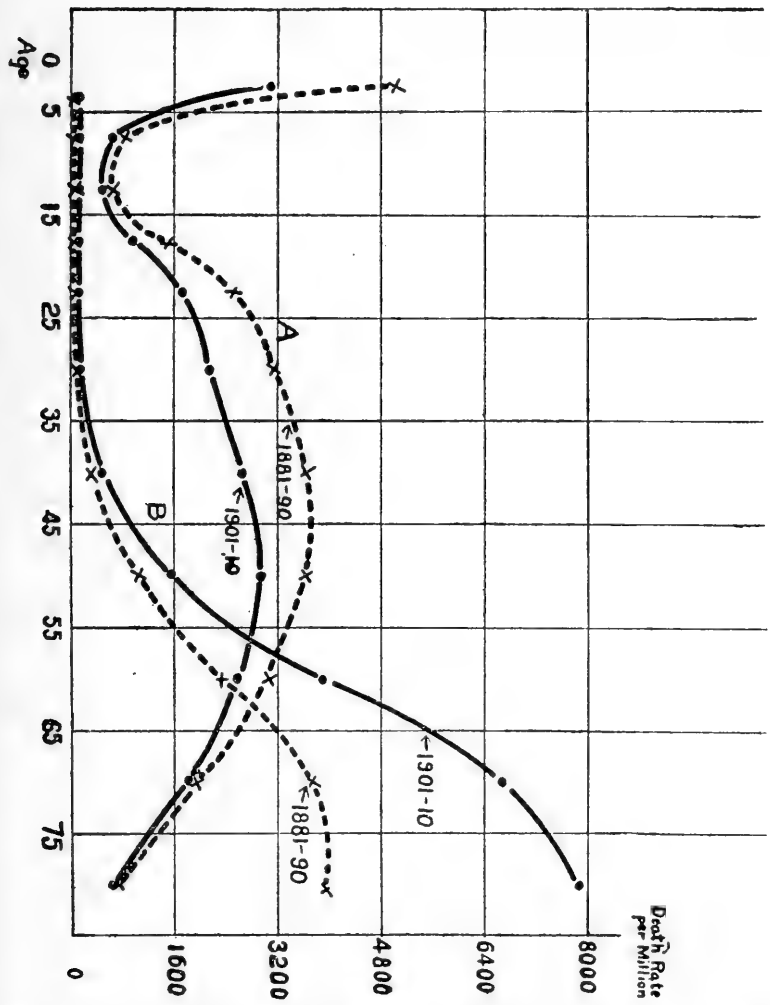

FIG. VI—DEATH RATE PER MILLION MALES AT DIFFERENT AGE PERIODS IN 1881-90 AND 1901-10.
A.—Tuberculosis (all forms).
B.—Cancer.

under risk) for each group of diseases, the maximum increase being at ages 65-75 and at 75 and upwards. To what extent this increase is real, and to what extent it arises from more

accurate medical diagnosis and certification of the cause of death, cannot be stated with a high degree of probability; but it must be borne in mind that this increase is associated with a reduction in the death-rate from all causes in the aggregate at these very ages. The only absolutely certain facts are that on the average in English experience we live longer than in the past; but those who do not die literally of old age are certified in a larger proportion than in the past to have died of circulatory and renal diseases.

TUBERCULOSIS

The curves of English experience in 1881-90 and in 1901-10 for tuberculosis shows the decline in the death-rate from this supremely important disease; also the gradual postponement of the age of maximum death-toll from it. We are more immediately concerned in this paper with mortality after middle life, and the curves bring out the too little remembered fact that tuberculosis remains one of the chief causes of death right up to old age.

CANCER

It would require a separate lecture to discuss the question of increase of cancer. The balance of evidence appears now to support the view that cancer of certain organs has increased, although Professor Willcox, bringing up to date a paper by Mr. George King, F.I.A., and myself****, has recently come to the conclusion tentatively reached by us in 1893.

In this earlier paper, the national returns from each division of the United Kingdom were subjected to accurate analysis, and statistics were given based on the death-rate of Frankfort-on-the Rhine for 1860-89, showing the incidence of cancer according to site. The conclusion reached was that the apparent increase of cancer is confined to "inaccessible" cancer of difficult diagnosis; and Professor W. F. Willcox has continued his comparison of cancer death-rates in Frankfort down to 1913, with the result of confirming the earlier observations. The subject has been rediscussed

****"On the Alleged Increase of Cancer (Proc. Roy. I. Soc., Vol. 54. 1893)

Diarrheal Diseases

in much detail by Dr. T. H. C. Stevenson in the annual report of the English Registrar General for 1917, in the light of English cancer data giving localization of the lesion; and the conclusion he reaches is that in England "amongst males mortality from accessible cancer has increased more rapidly than from inaccessible, whereas amongst females the position is reversed, the result for both sexes jointly being a moderate excess of increase from inaccessible cancer."

In other words, the English figures do not support the conclusion drawn from the Frankfort figures, which at the time they were examined were the only figures available. Whether cancer mortality is increasing or not, the practical point is that from middle life onwards it is one of the chief causes of premature mortality.

So far we have seen that a remarkable increase has occurred in the registered death-rate at ages over 45 from certain diseases; and that this is associated with a declining death-date from all causes in the aggregate at these ages. The absence of a corresponding decline in the total death-rate at these higher ages in the registration area of the United States is better explained by immigration of a diverse population, than by the assumption that causes of degeneration are operating in the native born population of the United States to an extent beyond that in England. Of course, this does not imply that the conditions causing "degenerative diseases" do not require appropriate action in both countries. The English Registrar General, in his Decennial Supplement for 1901-10 gives valuable tables of the death-rate at various ages from 32 of the chief causes of death. From these tables the diagrams already given comparing the experience of 1881-90 and of 1901-10 for

Pneumonia
Bronchitis
Tuberculosis
Cancer
Cardiac Diseases
Renal

have been taken.

In the twenty years between the two periods the chief causes of death which showed decrease and increase, respectively, were as follows:—

CAUSES OF DEATH

Group I. Decreasing	Group II. Increasing
Smallpox	Influenza
Measles	Diphtheria
Scarlet Fever	Diarrheal Diseases
Whooping Cough	Pneumonia
Croup	Cancer
Enteric Fever	Diabetes Mellitus
Syphilis	Valvular Diseases of Heart
Tuberculosis	Endocarditis
Rheumatic Fever and Rheumatism of the Heart	Nephritis and Bright's Disease
Meningitis	Suicide
Epilepsy	
Laryngitis	
Bronchitis	
Pleurisy	
Violence	

In supplement of the evidence already stated, the following diagram may be studied. In A the age distribution is shown of the male death-rate from all the diseases in Group I, above, in 1881-90 and 1901-10, respectively. In B are displayed the corresponding facts for Group II; while in C is shown the age-distribution of the total male death-rate from all other causes in the two decennia.

We thus see, as has already been displayed by the life-table method, that the balance is on the side of gain of life. For England we must decide between two possibilities. Either increased mortality from certain diseases in midde and advanced life has been more than counterbalanced by decreased mortality from other diseases; or there has been merely transference of entries owing to gradually increasing accuracy of certification of deaths; or these two factors are represented in the results to an uncertain extent.

For the registration area of the United States the situation is not so clear. As in England, there has been great increase in the registered mortality from certain diseases during middle and

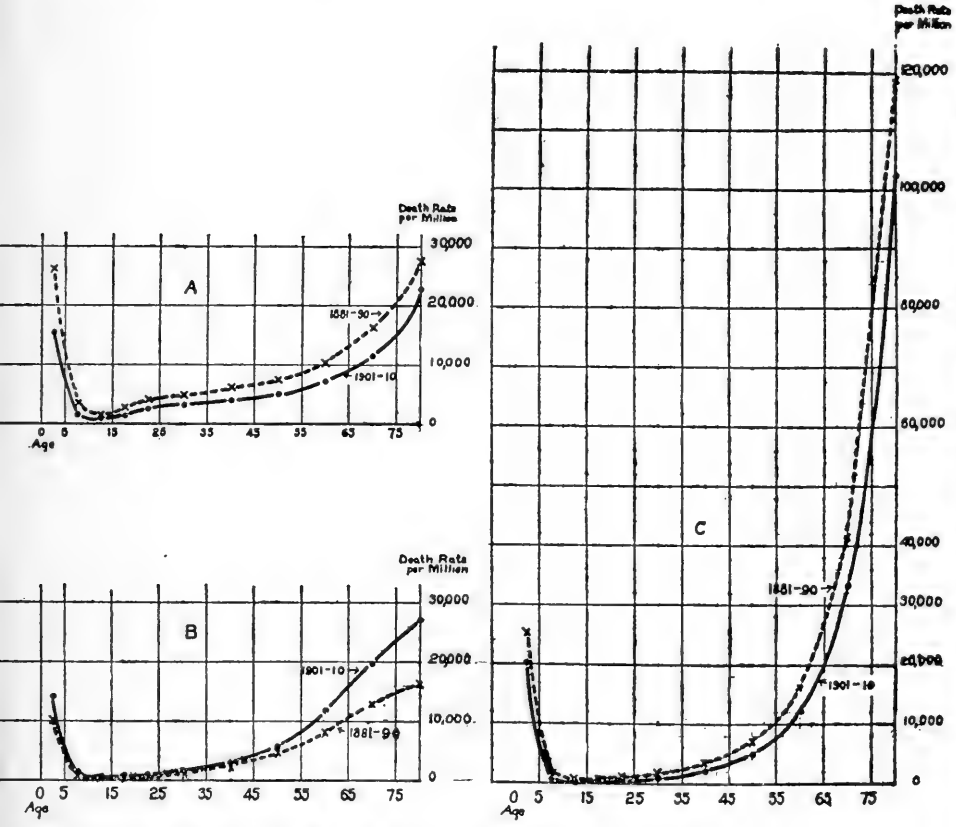

FIG. VII.—DEATH RATE PER MILLION MALES AT DIFFERENT AGE PERIODS IN 1881-90 AND 1901-10.
A.—Group of diseases with decreasing death rate.
B.—Group of diseases with increasing death rate.
C.—All other causes of death.

late life. Thus, Dr. Frederick L. Hoffman in a paper on "The Mortality from Degenerative Diseases," while deprecating hasty conclusions from imperfect data, gives tables from which the following extracts are taken:—

PERCENTAGE INCREASE OR DECREASE IN THE DEATH-RATE FROM ALL CAUSES AND FROM EACH OF THE FOLLOWING DISEASES BETWEEN 1900 AND 1915.

	At Ages 30-40	40-50	50-60	60-70	70-80
Apoplexy and Cerebral Softening	+29.4	+11.1	+18.8	+33.3	+39.7
Heart and Arterial Diseases	+ 6.3	+19.8	+30.0	+56.3	+81.7
Kidney Diseases	+21.0	+ 1.8	+22.2	+43.0	+64.1
All Causes	—22.6	— 8.5	+ 0.9	+ 5.8	+ 4.2

The total death-rate from all causes at ages over 45 has also increased among males in the registration area, though to a relatively small extent. Furthermore, the prospects of survival to old age in this area are on the average equal to those of the English population; and it is likely that the increased death-rate from all causes and from these "degenerative diseases" is due to the introduction of foreign populations, who have lived in youth, and possibly after arrival in this country, an arduous life of overstrain under circumstances of lower civilization with excess of infective diseases.

It would be foolish, in view of the above broad facts, for the average population, to commit oneself to a pessimistic view as to middle and late middle life in the future either for the English or the American white population. A more favorable view is, however, not incompatible with the existence of circumstances favoring, or even producing, premature decay in special groups. But these circumstances do not exist to an increasing extent, or are more than counterbalanced for the mass of our populations, who chiefly determine the trend of our national statistics; and it is all the more satisfactory—especially from a public health standpoint—that this should be so, in view of the increasing trend towards city life.

POSSIBILITIES OF DIMINISHING DISEASES AT AGES 40 TO 70

There is ample evidence to show that, apparently irrespective of modes of life, longevity is the rule in certain families; while

in others, equally apart from perceptible differences in mode of life, the arteries fail prematurely. It would appear that there is no condition in which the influence of heredity is more marked than in the capacity to attain old age.

Apart from this unequally distributed inherent capacity for old age, we must, if asked to state in a single formula the most serious impediment to the attainment of old age, agree that

INJURY DUE TO INFECTIONS IS THE CHIEF CAUSE OF MORTALITY

Next to infections, as a cause of premature death, comes malignant disease, the most pitiless of enemies, depriving us by cruel steps of those whose ripe judgment and mature knowledge make them almost irreplaceable. It is between the ages of 40 and 60 that men begin to repay the community for the varied expenditure hitherto incurred on them. Prior to this the balance is often on the wrong side; and it is at these ages that cancer chiefly claims its victims.

In men in England at ages 45-55, one death out of 10.5 total deaths from all causes; at ages 55-65, one death out of 8.1; at ages 65-75, one death out of 9.6; and at ages over 75, one death out of 19.3, total deaths were due, in 1901-10, to this cause. And it still remains true that, although in every civilized country earnest investigators are searching for a line of action which may be hopeful, if not certainly successful, at present we can only point to the importance of avoiding protracted local irritations, and to the essential value of early diagnosis and treatment of the disease, as competent to prevent death in a certain proportion of cases.

We must confess our almost equally great inability in respect of catarrhal infections, whether ordinary catarrhs, or their more serious congeners, bronchitis and pneumonia. Apart from avenues of hope in respect of pneumococcic infections, there is little prospect of early conquest over these diseases.

Pandemic influenza, with streptococcic secondary infection, has recently proved to be a more serious cause of death than a world war; and no action for its abatement, on a large scale, has been practicable.

Tuberculosis, although capable of being reduced to a shadow

of its present importance—were we prepared to invest the necessary money and energy in continuous and complete action against it—still stalks the earth, and cuts off a large share of our population, especially at ages when they are only beginning to repay their communal indebtedness. Tuberculosis is also, much more than is recognized, a common cause of death at ages over 50, either as a chronic disease, often masquerading as senile bronchitis, or as an acute complication of other diseases.

As tuberculosis becomes relatively less serious, then cancer more than takes its place as a cause of premature mortality.

Diseases of the heart and blood vessels form a complex group, and have diverse causation. Of the evil influence of excessive muscular work, of over-feeding, alcoholism, or excessive smoking, or other unhygenic personal habits in securing prematurely senile arteries and heart, I will assume that there is no doubt; but it is practically certain that such factors are of relatively small importance as compared with the havoc played by the multiple infections to which we are subjected. The chief enemies which prevent our arteries and heart from fulfilling their duties to a robust old age are the specific infections of rheumatic fever, of syphilis, the pneumococci, and various streptococci from focal or other infections, and still oftener secondary to an attack of an acute specific infectious disease.

We are now thoroughly advised of the magnitude of the mischief done by syphilis. Cerebral hemorrhage before the age of 40 or 45 may be assumed nearly always to owe its origin to this disease; and we know that more than one-tenth of the inmates admitted to our lunatic asylums are there owing to syphilis, and die a premature death because of this infection. Will the community have the courage and wisdom to adopt the medical, police, social and moral measures required to reduce it to insignificance?

It must be confessed that but little more appears to be known concerning rheumatic fever than when in the Milroy Lectures for 1895 * I showed by elaborate mortality and sickness statistics derived from the general mortality experience of different European countries, from general notification experience of Scandi-

* Lancet, May 9th and 16th, 1895.

navian countries, and from the experience of large general hospitals in England and other countries, that rheumatic fever is an epidemic disease, of which widespread epidemics occur at intervals of a few years, though in the intervals it is never entirely absent from most communities. I drew attention to pandemics of rheumatic fever, particularly those of 1868, of 1874-75, and of 1884. I also showed that in England the epidemic prevalence of rheumatic fever in the period for which records are obtainable has always occurred in years of exceptional scarcity of rainfall.

The causation of renal diseases or of arterio-sclerosis, apart from the influence of acute infectious diseases, is still obscure. We can, however, assert with a high degree of probability that if rheumatic fever could be avoided, if syphilis could be eliminated, and if the acute and chronic infectious diseases of childhood and youth and early manhood could be reduced to a shadow of their present dimensions, there would result an immense leap forward in the standard of health of the general community, and in the number of persons attaining a stalwart and healthy old age.

The chief and most promising line of attack on the disabling diseases of middle life, and even of higher ages, consists in the adoption of all known preventive and curative medical measures in childhood and in youth, adolescence and early manhood. It is chiefly in these years that the bill is incurred which has to be paid two, three or four decades later. This does not imply, of course, that efforts made to anticipate and retard the onset of illness in older persons are fruitless. They are very desirable.

We have in fact a quadruple line of action open to us in securing a healthy life of physiologically normal duration:—

1. To pursue the present lines of public health activities with complete efficiency, and thus reduce the prevalence of the infectious diseases (chronic and acute), which, though now controllable, are not controlled.

2. To undertake every additional line of public and private control of disease in the first twenty-five years of life, which our more recent knowledge of preventive medicine shows to be practicable.

3. To adopt the same measures so far as they are applicable to ages over 25.

4. To follow every line of investigation which may enable us to secure further control over disease.

There can be no doubt that, although every line of action indicated above must be followed to ensure success, the greatest and earliest results will be occurred by a great increase of activities under the first two of these headings.

WITH INCREASE OF AVERAGE LENGTH OF LIFE HAS THERE BEEN IMPROVED HEALTH?

The facts already stated prove not only that out of a given number born a larger number than formerly survive to the more useful years of life and to old age; but that out of equal numbers taken at age 25, or even at age 40, the prospects of survivorship to old age have improved. Any doubt on this point, for the white population of the United States, results probably from the vast introduction of a foreign population belonging in large measure to a lower order of sanitary and social organization.

But these facts are not incompatible with the possibility that increased survival means a large amount of invalidism and inferior health in the population. Are we in the fullest sense living longer, or are we merely longer in dying? This problem cannot be discussed adequately in the present paper. I may be permitted to quote the following remarks written by me in 1893. At that time the death-rate had increased at the higher ages, as it has recently done in the United States. But the general comments are relevant still.*

(1.) "A favorite explanation of the diminished expectation of life in adult years is that, owing to the saving of life in the earlier years of life—a saving which has been especially in zymotic diseases and phthisis and other tubercular diseases—there has been a larger number of weakly survivors, who would under the former regime have been carried off by these diseases. In other words, the operation of the law of the survival of the fittest has been impeded, with results unfavorable to the health and vigor of adult life. This argument assumes that weakly children are more prone to attack

* The Brighton *Life-Table*, 1893, or *Elements of Vital Statistics*, p. 316.

by infectious diseases than robust children, an assumption which experience does not confirm. These diseases appear to attack the majority of children, weakly or robust, who are exposed to their infection. It might be reasonably expected, therefore, that with a decrease in the total deaths from infectious diseases, there would have been at least a corresponding decrease in the number of those who are left maimed by an attack of one of these diseases to survive to adult life. I personally think that the weeding out of weakly lives, caused by the greater mortality among weakly children suffering from an infectious disease, is almost entirely counterbalanced by the greater number of children made weakly in former times by non-fatal attacks of an infectious disease.

The case for deterioration of the race by survival of patients who would formerly have died in early life from phthisis and other tubercular diseases, appears to be a stronger one. It is probable that a larger proportion of phthisical patients are cured than formerly. It is probable also that many more children with a strong tendency to phthisis, or even suffering from its early symptoms are prevented by the improved medical treatment and the improved social conditions of recent years, from developing the disease. These now may survive to adult life and become the parents of children with a strong tubercular tendency.

Such a fact need not, however, cause any serious apprehension for two reasons. In the first place, hereditary tendencies to phthisis only act under favorable predisposing conditions, such as damp and overcrowded houses, sedentary occupation in a cramped position, etc.; and in presence of the active exciting agent, the specific bacillus to which phthisis and other tubercular diseases are due. The exciting cause of tuberculosis is the introduction *ab extra* of the specific infection by inhalation or by means of food.

In the second place, assuming that more phthisical patients survive than formerly, is it not equally true that fewer persons *become* phthisical than formerly? With a diminution of the active cases of phthisis, the number of centres for phthisical sputum, the chief cause of subsequent infection, must have diminished to a corresponding extent. Of the fact that the predisposing causes of phthisis-damp and overcrowded houses, ill-ventilated workshops, etc.—are steadily diminishing, there is evidence on every hand. It is, therefore, reasonable to suppose that much at least of the deteriorating effect of the survival of tubercular persons is counter balanced by the large number of persons who are *prevented by improved sanitary and social conditions from becoming tubercular.*

It is premature at present to attempt by statistical means to determine how far the counteracting influences which are at work, balance each other, or failing a balance, on which side is the preponderating effect.

(2.) The increased stress of modern life is supposed by many to explain the increased death-rate among adults. It is doubtful if such increased

strain exists in the community as a whole. Each adult as he becomes year by year more deeply involved in the battle of life, comes to the conclusion that the general strain of life in the community is increasing, forgetting that the same causes operated as life advanced in previous generations. There is reason for thinking with Dr. Pye-Smith that much of the evil ascribed to "over-pressure" is really due to over-feeding and drinking.

Assuming, however, that over-pressure exists in certain stations of life, e. g., among city merchants, medical men, etc., it cannot be said to exist generally among professional men. Clergymen, lawyers and civil-servants are as classes long-lived.

Even assuming that over-pressure exists throughout the whole of the professional and mercantile classes, these do not form the mass of the community. *The majority of the population of England and Wales belong to the wage-earning classes*, and the conditions of these classes will therefore necessarily have the greatest influence on the total result.

Those conditions, as we know, have greatly improved.

I see no reason for altering the view stated in the preceding extract, except that I should now attach less importance to hereditary predisposition in tuberculosis, and should state my conclusions with less hesitation. Under the circumstances of modern civilization the assumption that natural selection can act as under savage conditions is completely unwarranted. Civilized life, leading to progressive improvement of environment and of personal habits, submerges any possible influence of natural selection in removing those unfit for survival, substituting for it a process of steady uplifting in fitness of the general population.

This is well illustrated in the following curves, which show that infants who have escaped the assumed selective influence of a high infant mortality in infancy continue to survive all through life in larger numbers, than infants among whom excessive infant mortality has prevailed.

The recent recruiting figures have been adduced as evidence of widespread physical deterioration, and they doubtless show that both in this country and in the United Kingdom a large proportion of recruits suffered from physical defect or disease, rendering them unfit for military service. I have no wish to minimize the importance of these figures. That they indicate

any deterioration in physique in the population, historically, is not proved and is highly improbable.

In 1844 over half the recruits in Leeds were rejected; and in Birmingham and the surrounding towns in 1852 only one-third of the men who enlisted were approved. We have always thought we were a decadent race, and so have other nations before us.

	Mean Population, 1891–1900.	Mean Infant Mortality per 1,000 Births.
England and Wales ...	... 30,643,479	... 157
Selected Healthy Districts ...	4,477,485	... 109

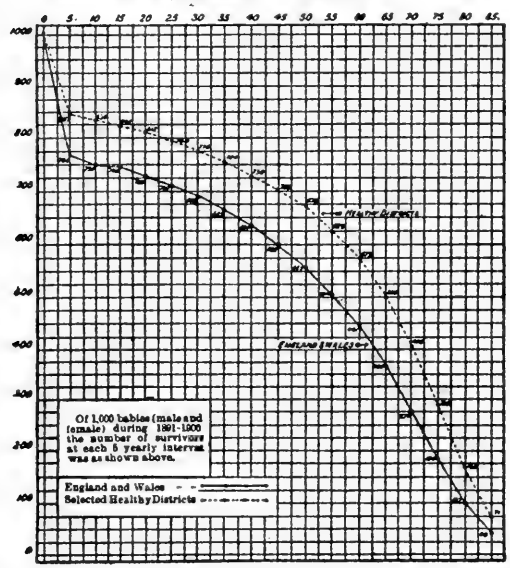

FIG. VIII.—Showing the number of survivors at each successive year of life out of 1,000 infants born in England and Wales and in selected healthy districts in 1881-90. This table is to be read as shown in the following example:—At age 20 the number of survivors was 812 in healthy districts, 726 in the country as a whole; at age 60 was 573 in healthy districts, 441 in the country as a whole; and so on.

The ancient Greeks thought themselves to be degenerate, and the Spartans adopted the ill-considered action of exposing weakly infants to avoid this result. Sophocles is quoted by Dean Inge as stating that the best fate of man is "not to be born, or being born, to die." Shakespeare refers to this "waning age," and has other similar passages. In 1721 Bishop Berkeley wrote an

"Essay towards preventing the ruin of Great Britain"; and you will remember Wordsworth's sonnet in which the following passage appears:—

"Milton, thou should'st be living with us at this hour
England hath need of thee;
She is a fen of stagnant waters"

He adds, however:—

"It is not to be thought of that the flood of British freedom.....
.....
That this most fatal stream in bogs and sands
Should perish; and to evil and to good
Be lost forever."

Every Tory squire still believes that England is going to the dogs; but I prefer the sanguine view expressed by Tennyson as embodying the real outlook of both England and America:—

"This fine old world of ours is but a child,
Yet in the go-cart."

KIDNEY FUNCTION*

DR. A. N. RICHARDS

Professor of Pharmacology, University of Pennsylvania

THE subject assigned to me, Kidney Function, is far too broad for discussion within the permissible limits of one lecture. I therefore propose to restrict what I have to say to the subject:

Glomerular Function and the Modes of its Regulation.

What I have to present is based upon work which has been proceeding with interruptions in the Laboratory of Pharmacology of the University of Pennsylvania for a number of years past; this work has been jointly carried on by Dr. O. H. Plant and myself during the years 1915 to 1920, and by Dr. Carl F. Schmidt and myself from September of last year until now. Their collaboration has been invaluable.**

1. Evidence that the Glomerulus of the Kidney is the Chief Structure concerned in the Renal Elimination of Fluid from the Blood.

Until the classic work of the English anatomist, William Bowman, published in 1842, there was no convincing evidence that connection existed between the Malpighian bodies and the uriniferous tubules. By extraordinary skill in dissection, Bowman proved that the capsule of the Malpighian body is the expanded extension of the membrane of the tubule. His first identification of the complete unit of structure by which urine is formed must therefore be regarded as the beginning of modern study of renal function.

Appended to Bowman's very complete description of the vascular arrangements of the kidney is a theory of the parts played by tubule and glomerulus in the formation of urine. He laid emphasis upon the structural similarity of the epithelium of

* Delivered February 26, 1921.

** The results of this work will shortly be published in the American Journal of Physiology.

the tubules and that of secreting glands, and drew the inference that the tubules eliminate from the blood "the peculiar principles found in the urine." He laid equal emphasis upon the dissimilarity of structure of tubules and capsule and stated his conception of the significance of this dissimilarity in these words, which, though frequently quoted, may well be repeated (1):

"Thus the Malpighian bodies are as unlike as the tubes passing from them are like the membrane, which, in other glands, secerns its several characteristic products from the blood. To these bodies, therefore, some other and distinct function is with the highest probability to be attributed. The peculiar arrangement of the vessels in the Malpighian tufts is clearly designed to produce a retardation in the flow of blood through them. It would indeed be difficult to conceive a disposition of parts more calculated to favor the escape of water from the blood than that of the Malpighian body. A large artery breaks up in a very direct manner into a number of very minute branches, each of which suddenly opens into an assemblage of vessels of far greater aggregate capacity than itself, and from which there is but one narrow exit. Hence must arise a very abrupt retardation in the velocity of the current of blood. The vessels in which this delay occurs are uncovered by any structure. They lie bare in a cell from which there is but one outlet, the orifice of the tube. This orifice is encircled by cilia in active motion directing a current towards the tube. These exquisite organs must not only serve to carry forward the fluid already in the cell, and in which the vascular tuft is bathed, but must tend to remove pressure from the free surface of the vessels, and so to encourage the escape of their more fluid contents. Why is so wonderful an apparatus placed at the extremity of each uriniferous tubule if not to furnish water to aid in the separation and solution of the urinous products from the epithelium of the tube?"

This is the first suggestion, founded it is true, upon teleological argument from structure, that the glomerulus is the chief site of fluid elimination in the kidney. This suggestion developed into universal belief. The experiment which established its truth was not made until 1878 when Nussbaum (2) performed the operation in frogs of ligation of the renal arteries. This excluded the glomeruli from the circulation but, owing to the double blood supply of the frog's kidney, did not abolish circulation in the vessels of the tubules. The result of this ligation was cessation of urine elimination.

This observation, confirmed by others (3), nearly approaches

to direct proof of the assumption made by the older anatomists. Since it is completely in harmony with considerations of structure, since it is supported by a mass of less direct evidence obtained in other ways and since there is no opposing evidence so far as I am aware, we may regard this question, so fundamental to all further study of kidney function, as satisfactorily settled.

II. The Nature of the Process by which Fluid is Separated from the Blood in the Glomerulus.

In Bowman's statement of his hypothesis that the glomerulus separates water from the blood, no clear idea is given of the nature of the process. Unaware of the epithelium which covers the glomerular tuft, he regarded the capillaries as projecting naked into the capsule, and he speaks of the cilia at the orifice of the tubule as presumably having power of diminishing pressure on the capsular side of the capillary tuft and so facillating escape of fluid from the blood. It seems to me that his words vaguely indicate the escape of fluid because of pressure within the capillary vessels.

There is no such vagueness, however, in Carl Ludwig's statement made in 1844, of his conception of the process (4). Using the anatomical facts demonstrated by Bowman and confirmed by himself, and applying principles of hydraulics, he stated that a significant pressure must be exerted by the blood within the glomerular capillaries upon their walls and that this pressure must result in the filtration of a certain amount of fluid through them. He assumed that the membrane through which the fluid passed was normally impermeable to proteins, fats, and to salts which might be combined with these, and hence that the urine as formed in the glomerulus is a protein-free filtrate containing blood crystalloids in the proportion in which they exist free in the blood.

I have no wish to enter in great detail into a discussion of the evidence for and against the filtration theory: it has been adequately reviewed many times and forms part of current physiological teaching. Since, in the development of what is to follow, an appreciation of the chief elements of strength and of weakness in the filtration theory is necessary, I make no apology for briefly

presenting the most important facts. The question whether the glomerulus filters fluid or secretes fluid is more than academic. A well based conviction that the understandable process of filtration is the chief factor of glomerular activity permits clearly defined views concerning the nature of alterations in glomerular function which occur in health and disease. It carries with it as an inevitable corollary a conviction of reabsorption of both water and dissolved substances from the lumen of the tubule; for no other process could account for the difference in composition between a blood filtrate and the urine as it leaves the kidney. Absence of such conviction on the other hand necessitates refuge in the conception of "secretion," a word implying ignorance or uncertainty of processes involved and ill-defined point of attack on the further questions of alterations in renal function.

There are three groups of experiments which, I think, form the chief support of the filtration theory.

First, experiments which demonstrate the parallelism between urine elimination and renal blood pressure. These include the experiments in Ludwig's laboratory by Goll, (5), showing that changes in general arterial blood pressure, induced by vagus stimulation, hemorrhage, injection of blood, or ligation of large arterial trunks caused changes in a similar sense in urine flow; and those by Hermann (6) in which diminution in urine was found to follow partial obstruction of the renal artery. They include also numerous experiments which developed from Claude Bernard's discovery of vasomotor nerves — experiments in which the nerve supply of the kidney was either divided or stimulated and resulting increase or decrease in urine found to be attributable to dilation or constriction of the vessels in the kidney (7). It was recognized by Ludwig and his colleagues that such changes in the renal circulation as were studied in these experiments, involved alterations not only in renal blood pressure but in velocity and volume of renal blood flow as well. Reasons were adduced (Hermann) for belief that the effective variable in these experiments was that of pressure. The force of the experiments and the influence of Ludwig was such that his conception of glomerular

filtration and tubular reabsorption became the generally accepted view (8).

The second group of experiments to which I refer is based upon this principle of physics; that in order to separate a dissolved substance from its solvent by filtration through a membrane, permeable by the solvent but not by the dissolved substance, filtration pressure must be greater than the osmotic pressure of the dissolved substance. Tammann of Rostock in 1896 showed that the osmotic pressure of all the substances dissolved in the blood plasma was nearly 8 atmospheres (5840 mm. Hg) (9): that the osmotic pressure of the organic solids of blood plasma amounted to 840 mm. Hg. (He regarded the osmotic pressure of proteins as negligible.) Since no pressures of this order of magnitude are to be found in the animal circulation he concluded that the only substances of plasma which could physically be held back in the glomerulus are the proteins; hence the fluid separated in the glomerulus must be the water of the blood containing all dissolved substances except proteins.

Starling, in the same year (10), discovered that the osmotic pressure of plasma proteins amounted to 30-40 mm. Hg. He showed that a force of this magnitude exerted by substances retained within the blood vessels was sufficient to explain in part the absorption of fluid from tissue spaces into the blood vessels. In 1899 he extended this reasoning to the explanation of glomerular function (11). By improved method he redetermined the osmotic pressure of plasma protein and obtained the figure 25-30 mm. Hg. If the osmotic pressure of plasma protein is the force which blood pressure must overcome in order to filter fluid from the blood in the glomerulus, then it should be found that the lowest arterial blood pressure compatible with urine elimination is slightly above this. His own experiments and those of many others showed that urine ceased to be eliminated when arterial pressure fell below 40 mm. Hg. Further, if glomerular function is filtration, then the difference between arterial blood pressure and the maximum pressure in the ureter against which

urine can be eliminated should be almost that of the osmotic pressure of the proteins. He found this difference, during profuse diuresis in the dog, to be 32-43 mm. Hg. These results, confirmed and extended by Knowlton (12), are so completely in accord with the demands of the filtration theory that they furnish the strongest support for it.

The third group of experiments in this connection are those of Barcroft and Straub (13), made in 1910. They applied to the kidney the methods so fruitfully developed by Barcroft for estimating the rate of metabolism of organs. Saline diuresis—i. e., diuresis following the injection of sodium chloride solutions—was found to be unaccompanied by increase in utilization of oxygen or formation of carbon dioxide. Knowlton and Silverman later showed that this was true for diuresis following injection of pituitrin (14). The conclusion was drawn that physical factors rather than "vital" or "secretory" are concerned in this increase in kidney function, the inference being that filtration is increased.

These are the facts which to my mind most nearly constitute "proof" of the filtration idea: they are reinforced by considerations of the structure of the glomerulus and by observations in other directions; that the more rapidly urine is eliminated, the more nearly it comes to resemble a filtrate from the blood, that the glomerular fluid is alkaline as tested by intravital indicators, that the osmotic pressure and chloride content of the cortex more closely resemble that of the blood than does that of the medulla. This collection of facts led Bayliss to write in 1915 "the evidence for this (glomerular filtration) is overwhelming" (15): and Cushny, in his development of the "modern" theory of urine formation, to accept glomerular filtration as a fundamental truth (16).

It is easy to develop conviction of the truth of filtration by study of the work to which I have alluded. It is not so easy to hold it after consideration of some of the questions which have been put to the filtration theory and have not found satisfactory answer.

Heidenhain in 1874 began the publication of his work on the

kidney from which developed the so-called Bowman-Heidenhain theory. As is well known he injected indigo carmine into the circulation and failed to find traces of it in the capsule or any staining of glomerular structures by it. Since it was to be found in the lumen of the tubule and since the tubular epithelium was stained by it he was forced to conclude that it had been secreted by the tubules and had not been filtered by the glomerulus (17). This observation led him to further results which obliged him to deny the filtration-reabsorption theory completely and to attribute urine formation to secretory processes in the epithelium of glomerulus as well as of tubule; i. e., to processes not explainable by known physical or chemical laws.

Most of Heidenhain's contentions have since been successfully met by adherents of the filtration idea; Cushny's monograph contains an admirable exposition of this subject. One objection, however, seems to me to have been least satisfactorily answered and it happens that this is the one to which Heidenhain himself attached the most weight. It concerns the effects of compression of the renal vein upon urine elimination. The following is a translation of his own words (18).

> But if mechanical filtration does really occur, then elimination of water must always increase with the pressure. An old experiment shows that this is not so. For if the pressure in the glomeruli is increased by partial or complete occlusion of the renal vein, an immediate diminution in urine occurs.
>
> This fact contradicts the pressure hypothesis in the most abrupt (schoffstem) manner.
>
> If it is considered that increase in aortic pressure, if only a few mm., often causes a considerable increase in urine, and that after partial or complete occlusion of the renal vein a considerable rise of pressure within the glomerular vessels must occur, then it is apparent that here is a phenomenon completely unexplainable by the filtration hypothesis.

Ludwig was aware of this objection and had met it by demonstrating that complete obstruction of the renal vein in the living animal caused such swelling of the veins within the kidney that the tubules were compressed and their lumina obliterated (19). Obviously no urine could issue from the kidney under these circumstances. It appears that Heidenhain accepted Lud-

wig's demonstration of the effects of complete occlusion (20), but he did not regard it explanatory of the events which follow partial closure of the vein. Slight obstruction, of a degree sufficient to lessen, but not to suppress, urine flow could not cause such lessening by engorgement of veins with resulting closure of tubules. The fact that urine continued to flow, though at a lower rate, indicated that the tubules were patent. Paneth's later experiments (21), showing the possibility of diuresis by sodium nitrate during constriction of the renal vein, confirmed this conclusion. For this reason Heidenhain regarded the failure of slight compression of the renal vein to increase urine flow as the strongest argument against the filtration hypothesis and it was this that led him to the belief that the velocity of blood flow through the glomerulus, rather than the pressure of blood within it, was the determining factor in the first formation of urine in the kidney.

In answer to this objection it was pointed out by Tammann (9) that if the fluid is filtered from the blood in the glomerulus, any stagnation of flow in the glomerulus, as by venous obstruction, would lead to rapid increase in osmotic resistance to filtration. It has not been shown that this factor can be so effective during partial occlusion of the vein as to more than compensate for the increased glomerular pressure. It has been suggested by De Souza (22) that blocking of the renal vein causes reflex constriction of renal artery, but no evidence of this has been presented, so far as I am aware. Consideration of these matters leads me to think that the argument against filtration based upon the effects of obstruction of the renal vein has not been adequately answered.

Another series of obstacles in the way of unreserved acceptance of the filtration hypothesis has arisen from the comparison of urine elimination with vascular conditions in the kidney as shown by oncometer records of kidney volume; and these difficulties have increased with the later development of improved methods of estimation of flow of blood through the kidney.

The oncometer, first applied to study of renal physiology by Roy and Cohnheim in 1883, registers changes in the total volume

of the kidney: these changes are commonly referred to alterations in the state of the renal blood vessels. In 1901 Gottlieb and Magnus (23) made an admirable series of observations on blood pressure, kidney volume and urine flow during diuresis. Following the injection of single doses of diuretics, remarkable parallelism between urine elimination and vascular dilatation as shown by the oncometer was observed: but when repeated dosage was given this parallelism failed. Diuresis was observed to increase in some instances at a time when renal vessels, as shown by the oncometer, were constricting; in others it diminished while renal vessels were similarly shown to be dilating.

These objections were materially supported by the late Professor Brodie of Toronto. He extended the observations of Magnus and Gottlieb by including in his experiments direct estimations of blood flow through the kidney. In his lecture before the Harvey Society in 1910 (24) and in his Croonian lecture of 1911 (25), he stated that following the injection of diuretics, in five experiments, he had observed the following coincident phenomena:—Increased kidney volume (indicative of dilatation of vessels); diminished blood flow (indicative of constriction of vessels); increased urine elimination.

Both Magnus and Brodie apparently accepted the common implication of vascular changes; viz: that dilatation of renal vessels means rise of intraglomerular pressure, and constriction of renal vessels means decrease in intraglomerular pressure, and hence their observations became so self-contradictory when viewed in the light of the filtration hypothesis that they were forced to abandon it.

In the considerations thus far advanced I have hoped to show that in spite of the array of strength back of the belief that urine is first formed in the glomerulus by a process of filtration, sound observations exist, made by most competent observers, which have forced them to deny it. Concern over these difficulties, and the necessity of a conviction concerning them, led to a series of experiments by my colleagues and myself which have, we think, a direct bearing on their solution.

In Hermann's (second) paper (6) on kidney function pub-

lished in 1862 it is stated that "the effect of pressure changes as compared with other factors which modify urine excretion can only be brought out clearly when one has control over the blood entering the vascular system and can regulate it at will." I cite this to show that the desire for some sort of artificial experimental control over circulatory conditions in the kidney in order to reduce the number of variables in an experiment, is very old. Hermann devised a clamp by which the calibre of the renal artery could be narrowed, hoping to identify the effects of lowered renal blood pressure by this means: somewhat similar experiments have more recently been made by others. A defect in such experiments, recognized by their authors and emphasized by Heidenhain, is that such a device simultaneously alters both blood pressure and blood flow in the renal circulation and there is no direct means of distinguishing effects due to one of these to the exclusion of the other.

During the years 1912-14, C. K. Drinker and I designed and constructed an apparatus for the perfusion of isolated surviving organs, capable of pumping a pulsating stream of fluid in a manner similar, as pulse records showed, to that of the heart. (26). Its volume output was controllable within fairly wide limits. With it we perfused the dog's kidney and were able to show that the fluid which issued from the ureter was urine and not a transudate. In 1914-15 Dr. O. H. Plant and I elaborated a method for perfusing the rabbit's kidney *in situ* with this apparatus (27). Our method possessed these advantages and possibilities:

(1) The perfusion fluid was the undiluted blood of the animal whose kidney was perfused plus blood taken fresh from another animal of the same species. Hirudin was used to prevent clotting.

(2) The artificial circulation through the perfused kidney was inaugurated without any interruption in blood flow through the organ, and in some instances, urine flow continued without interruption during the change from normal to the artificial circulation.

(3) While the output of the perfusion apparatus could be

varied at will, for any particular adjustment the output was constant, regardless of the resistance offered by the vessels through which it drove the blood. It was thus possible to alter pressure by various means within the kidney vessels without simultaneous alterations in volume flow, or velocity of blood in them. It is in this respect that our experiments differed essentially from those of earlier workers. (28).

The means which we used to alter pressure in the circulation of the perfused kidney were these: stimulation of the splanchnic nerve; injection of adrenalin; partial occlusion of the renal vein.

Since all of these agencies raised pressure in the renal circulation and since the conditions of our experiment were such that they could not materially change the blood flow, we seem justified in attributing such results as were obtained to changes in renal blood pressure.

Each of the three agencies tested increased urine formation in a number of experiments practically without exception.

It will be noted that among these agencies employed is venous obstruction, which, in the intact animal always causes diminution of urine, a fact regarded by Heidenhain as the strongest argument against filtration. In our experiment, in which it increased urine, there was no stagnation of blood in the glomerular capillaries which might neutralize the effects of increased glomerular pressure as a filtering force. The experiment seems to me to remove the force of Heidenhain's objection and to confirm the suggestion that in the intact animal partial occlusion of the renal vein so lessens the rapidity of renewal of blood in contact with the glomerular endothelium that the effect of increased filtering force is nullified.

III. Regulation of Glomerular Pressure.

The experiments just described have served us in three ways: they yield evidence that rise of pressure alone in the renal circulation can cause increase in urine; they point to a solution of Heidenhain's difficulty which is consistent with the filtration theory; and they provide a point of departure for an analysis of the

effects of increased renal pressure. In this last connection, the action of adrenalin has been most useful.

If the vascular reaction of a perfused kidney to minute doses of adrenalin is compared with the same reaction of another structure, similarly perfused—e. g., the leg—a striking difference appears. Any dosage of adrenalin which causes constriction of the vessels of the leg also causes diminution in volume of the leg as shown by the oncometer. When a perfused kidney is similarly tested, it is found that *large* dosage of adrenalin causes a similar effect, i. e., constriction of vessels as shown by rise of perfusion pressure and shrinkage of volume of the kidney; but smaller doses, which still cause some degree of constriction of vessels as shown by the perfusion pressure cause either no change in or distinct swelling of kidney volume.

In this experiment with the kidney we have an apparent paradox of coincident constriction of vessels as shown by rise of perfusion pressure and dilatation of vessels as shown by swelling of the kidney.

The only reasonable explanation of this paradox which has occurred to us is this:—between the afferent and efferent vessels of the glomerulus is interpolated the distensible capillary area of the glomerular tuft. The walls of the afferent and efferent vessels both contain smooth muscle; both are supplied with nerve fibrils (presumably sympathetic) ending in contact with the muscle cells (29). If, under the conditions of our experiment, the efferent vessel were constricted, a passive rise of pressure must occur in the glomerular capillaries proximal to it and the distension of these, thus brought about, might cause swelling of the kidney. In support of this view we recall the generalization which Elliott's work has established, viz: that the action of adrenalin is equivalent to stimulation of sympathetic innervation: and we have an observation of our own, made with the frog's kidney which shows unmistakably that adrenalin has the power of constricting blood vessels peripheral to the glomerulus.

In the minds of many physiologists a certain stigma appears to attach to perfusion experiments with isolated organs, when the

attempt is made to apply results so obtained to the interpretation of events within the intact animal body. If it were possible to demonstrate constriction of the efferent vessel by adrenalin in the intact animal with associated diuresis the force and usefulness of the experiments just cited would be increased. Reason for thinking that this might be possible seemed to exist. The efferent vessel of the glomerulus is a narrower tube than the afferent vessel. A constrictor influence, acting alike on both, would therefore produce a greater increase in frictional resistance to blood flow in the smaller (efferent) vessel: for this reason it seemed probable that very minute amounts of constrictor substances might, by more effective constriction of the efferent vessel, produce simultaneously three effects in the intact animal: diminution in blood flow through the kidney by constriction of efferent vessel; increase in urine by increased glomerular pressure; swelling of the kidney by distension of the glomerular capillaries. The event showed that this combination could be demonstrated following minute, but clearly constrictor, doses of adrenalin and pituitrin.

These experiments seem to me to yield evidence not only that the glomerular process is filtration but also that intraglomerular pressure—filtration pressure—is regulated by the relative degree of constriction or dilatation of the afferent and efferent vessels. This latter belief is intimated in a statement by Ludwig in 1856.

> Since the afferent and efferent vessels of the glomerulus, as well as the roots of the renal vein, contain muscle within their walls, the possibility exists that the blood stream in the kidney changes according to the contractions of these muscles, even though the movements of the heart and the general circulation in the organism remain unchanged (30).

In connection with the action of constrictor substances, like adrenalin and pituitrin, it becomes apparent how it is possible for the same substances in different dosage to produce opposite effects. Minute amounts causing more effective constriction of the smaller efferent vessel may increase urine by increasing intraglomerular pressure: larger amounts by constricting both afferent and efferent vessels may diminish urine by decreasing ingress to the glomerulus and so lessening both intraglomerular pressure

and velocity of flow. The literature shows that small dosage of adrenalin may cause diuresis. Nothing is easier to determine than that larger doses cause partial or complete suppression of urine. Similar, apparently contradictory, evidence concerning pituitrin can be found.

Permit me now to revert to Brodie's statement of a group of occurrences which he regarded as completely inconsistent with the filtration theory:—diminished blood flow through the kidney, increase of kidney volume, increase in urine. This group of occurrences, as we think our experiments indicate, is precisely that which would be expected as a result of preferential slight constriction of the efferent vessel, and instead of being inconsistent with the filtration theory is demanded by it.

From this reasoning it would seem as though any substance which is constrictor to renal vessels should, in suitable high dilution, show evidence of diuretic power, unless it lowers general blood pressure or diminishes permeability of the glomerular membranes. This supposition is now being tested.

I am inclined also to suggest another generalization, based upon this evidence that intraglomerular pressure may be altered by more effective action of a substance upon the efferent than upon the afferent vessel. It concerns the action of arterial dilator substances in general. If it be agreed that glomerular urine is a protein-free filtrate from blood, then it follows that any substance, in solution in the blood, which causes dilatation of renal arterioles and which in part passes out of the blood with the glomerular filtrate must from these facts be potentially diuretic: for its effective concentration will be greater in the blood in the afferent vessel than in the blood in the efferent vessel; and its dilator action will be greater on the afferent than on the efferent vessel, and for this reason alone intraglomerular pressure must rise.

It should be noted that by effective concentration I mean concentration in relation to the colloids of the blood.

Without having the direct evidence to support this idea, I venture to present it, in the belief that it is applicable to the glomerular behavior of a large number of substances—water, urea,

the caffeine series, salts, etc., all of which are vasodilator and all of which, we believe, leave the blood stream as it passes through the glomerulus.

If we regard the renal arterioles as very sensitive both to constrictor and dilator substances, as they most certainly are, and if we admit the possibility of such preferential action as I, have indicated on either efferent or afferent vessel, we must see in this a very delicate mechanism whereby intraglomerular pressure and hence the first formation of urine is regulated in accordance with the chemical composition of the blood.

IV. Description of Glomerular Circulation.

In this description of experiments, both of our own and of others which concern the nature of glomerular function and its mode of regulation, an implication has been permitted which now appears to me to require correction. Its correction does not, I think, materially alter the force of the conclusions which have just been drawn, but it adds an element in the conception of glomerular regulation which may be of greater importance.

The kidney contains a great number of urine-forming units. The number of glomeruli in the cat's kidney has been estimated at 16,000: in the kidney of a dog weighing 11 kilos, 150,000: in the human kidney, 2,000,000 (31). For each glomerulus there is a tubule. It seems to me that it has been tacitly assumed in the great bulk of writing on kidney function that the circulation through all of these units is at least roughly uniform, that they take equal part in the sum of activities which made up the total function of the whole organ. I have found one explicit statement of another conception. In Hermann's first work (1859) on kidney function, he noted that the two kidneys may eliminate different amounts of urine, and he stated that it was simplest to assume that all parts of the kidney do not act to the same degree all of the time, that one part of the excreting surface may rest or be active, while another part is in reserve (32).

We have observations which indicate that this is a true conception.

In the development of the idea that glomerular pressure may

be regulated by the degree of constriction of its efferent, as compared with its afferent, vessel it became highly desirable that we get evidence as direct as possible concerning changes in size of the glomerulus during the action of adrenalin under controlled conditions of blood flow. In 1919 Krogh of Copenhagen published his extremely important paper on the behavior of capillaries in muscle (33). He used methods of direct microscopic observation of muscles illuminated either by transmitted or reflected light. It occurred to us that the use of the same method might enable us to see the glomeruli of the kidney in operation, provided we could find a kidney sufficiently translucent to permit a certain penetration of light rays. In September of last year Dr. Schmidt and I found that the frog's kidney fulfills this demand. When we focussed the light of an arc lamp or a 1000 watt mazda lamp upon the ventral surface of an exposed frog's kidney *in situ,* the low power of the microscope showed in the interstices of the radicles of the renal veins nests of capillaries which to our view and that of competent microscopists could be nothing else than glomerular tufts. It soon became possible to distinguish the outline of the capsule, in many cases the entrance of the afferent vessel, and in not a few instances the exit of the efferent vessel as well. Because not all of these structures had the same appearance and to prevent egregious error we spent some time in attempts to identify a certain group of glomeruli in the living kidney, to follow this group through processes of fixation and embedding in order to prepare a stained section which should contain the structures examined in the living kidney. With the aid of Dr. B. Lucke this was successfully done. This identification has given a sense of security concerning previous and subsequent observations which we might not otherwise have had.

When the lateral border of the ventral surface of the frog's kidney is observed in this way, the large renal veins and their tributaries are most prominent. Arterial branchings and the divisions of the renal portal vein, being deeper in the kidney are less obvious. Details of the tubules are commonly indistinct.

In the interstices of the veins are seen the glomerular tufts. They vary in size from 80 to 250 microns in diameter. Some show a great multiplicity of tortuous narrow channels, each of a diameter sufficient to permit passage of one red cell. The capillary wall is not easily seen. Blood flow through these channels is oftentimes bewilderingly rapid. In other instances the appearance is of another type; instead of a multiplicity of channels, only one or two capillary loops are visible, these have wider diameter and show sluggish flow of more densely packed corpuscles. In the more slowly flowing blood streams pulsations are apparent; in the more rapidly flowing stream they may not be. Between these two extremes intermediate variations occur.

Concerning the problem which was the impetus for beginning these observations—i. e., the question whether the glomeruli could be seen to swell as a result of the constrictor action of minute amounts of adrenalin upon the efferent vessel—the answer is still indeterminate. A series of measurements by Dr. Schmidt of glomerular diameters before, during and after the injection of doses of adrenalin of the order of 0.1 cc. of 1:1,000,000 showed swelling, and in so far were confirmatory of our conclusions drawn from the mammalian experiments. But since a distinct improvement in the general circulation resulted from this injection the increased glomerular size may have been due to this. Before a final answer can be obtained, the experiment must be performed on the kidney, perfused with blood at a constant rate. This experiment has not yet been made. Other features of the glomerular circulation seemed to demand more immediate study.

In our earliest experiments the variability of our preparations was striking. In some preparations as many as eight glomeruli could be counted in a field of 2 mm. diameter; in others only three or four in the whole kidney in so far as it was accessible to inspection. Our frogs were pithed and if two or three drops of blood were lost in this operation the number of glomeruli to be found in the kidney was small. If, however, such a frog were immersed in a saline bath or if his abdominal cavity were filled

with isotonic salt solution, the number of visibly active glomeruli increased.

Acting on the suggestion which this fact afforded, we have made a series of counts of the glomeruli which show active circulation under varied conditions.

Bits of silk thread were laid transversely across the surface of the kidney at approximately equal distances of about 2 mm. (the diameter of our low-power field.) From five to eight fields were thus separated for ease in counting. A bit of cover slip was lightly laid over these, both to prevent displacement of threads and to avoid surface glare.

I shall cite figures to show alterations in number of glomeruli in which blood was flowing, before, during, and after the introduction of various substances to be mentioned.

1. *Isotonic salt solution.* As has been mentioned, salt solution is absorbed from the open abdominal cavity of the frog and as a result circulation improves if it has been lessened from hemorrhage. These figures illustrate:

Soon after preparation five fields showed 5 active, 8 inactive, total 13 glomeruli.

Thirty minutes after salt solution had been introduced into the belly the same fields showed 28 active, 0 inactive, total 28 glomeruli.

2. *Injection of blood.*—0.5 cc. of whole blood was taken from the aorta of one frog and immediately injected into anterior abdominal vein of a frog whose glomeruli had been counted. Before injection, active glomeruli 10, inactive 27, total 37.

5 minutes after injection, active glomeruli 39, inactive 9, total 48.

3. *Injection of isotonic salt solution.*—0.5 cc. of 0.6%. Before—41 active, 9 inactive, total 50. 10 minutes later, 54 active, 8 inactive, total 62. 20 minutes later, 44 active, 6 inactive, total 50.

4. Then *urea,* 0.1 cc. 20%. After—65 active, 2 inactive, total 67.

5. *Caffeine*—7 fields counted. Before injection 81 active,

11 inactive, total 92. 0.1 cc. 2% caffeine. 5 minutes later, 104 active, 0 inactive, total 104.

6. *Glucose*: 0.1 cc. 10% glucose: Before injection, 31 active, 12 inactive, total 43. Followed by progressive increase in number of active till 35 minutes after, 62 active, 3 inactive, total 65.

7. *Hypertonic Sodium Sulphate.* (5%) 0.1 cc. Before, 6 active, 0 inactive, total 6. After 13 minutes—51 active, 0 inactive, total 51.

8. *Adrenalin*: constrictor dose: 0.1 cc. 1:100,000: 3 fields. Before injection 49 active, immediately after 12 active, seven minutes later, 48 active.

9. *Pituitrin*: constrictor dose: 0.1 cc. 1:10 dilution of Pituitrin "S". Before—14 active, 5 inactive, total 19. After, 0 active, 16 inactive, total 16. Later 5 active, 12 inactive, total 17.

These and many similar observations have led to the conclusion that even under the most favorable of operative conditions, i. e., with the least loss of blood, all the glomeruli of the kidney of the frog do not receive blood simultaneously. Conditions which depress the circulation such as blood loss or destruction of the cord, or agencies which constrict blood vessels in the kidney, such as constrictor doses of adrenalin or pituitrin lessen the number of glomeruli which receive blood. Plethora, absorption or injection of isotonic salt solution, hypertonic NaCl, hypertonic sodium sulphate, urea, glucose, and caffeine—all are capable of impressively increasing the number of glomeruli which receive blood at one time.

Not only is the number of glomeruli showing active circulation altered by the agencies which I have mentioned, but also the number of capillary loops within a single glomerulus which take part in the capillary blood flow. Earlier in this section I referred to glomeruli of two rather widely different aspects in so far as blood flow through them is concerned: one in which narrow, rapidly flowing currents of blood indicate a complex net work of tortuous channels; others in which one or two loops only are visibly filled with blood and in these blood usually flows more

slowly and in a wider stream. The dilator agencies, urea, caffeine, etc., mentioned above have the power of transforming a glomerulus of the latter type into one of the former.

Adrenalin, on the other hand, in constrictor dosage, transforms a glomerulus showing a multiplicity of channels with rapid flow into one with fewer patent capillary loops and slow flow.

This indicates that just as all glomeruli in a kidney do not receive blood at once, so too in a single glomerulus, not all the capillary loops need be patent at one time. Dilator (diuretic) agencies increase the number of capillaries in the glomerulus through which blood is flowing; constrictor substances and depression of the general circulation lessen the number.

Another characteristic of glomerular blood flow in the frog's kidney is that it is not always continuous, but may be intermittent. Intermittence of glomerular flow is more apt to occur in a kidney showing active rapid circulation than in one in which blood flow is more sluggish. It was first observed by us in frogs after improvement of the circulation following absorption of salt solution; it has, however, been observed in frogs subjected to no other preparation than that required for looking at the kidney. The intermittence of blood flow may be of different types: in some instances there may be diminution in all and cessation in many at the same time, as though resulting from an influence outside of the kidney, as for example by changes in the general circulation or as a result of nervous stimuli to the blood vessels. This type is easily understandable.

What we think of, however, as true intermittence is less easy to comprehend: two adjacent glomeruli may be situated within a few microns of each other: blood flow in one may stop completely, to be resumed after an interval, without interruption or even perceptible alteration in flow in the other. This phenomenon may be multiplied so that in a favorable field one sees a lively series of irregular interruptions in flow through the various glomeruli visible.

The interruptions bear no relation to heart beat. The intermittence of one glomerulus was timed with a stopwatch—

15 seconds on: 12 seconds off 27 seconds on: 11 seconds off.

In another:

103 seconds on: 10 seconds off: 90 seconds on: 45 seconds off.

In another preparation, 5 glomeruli were watched at once:

Nos. 3, 4 and 5 stopped at the same time: Nos. 1 and 2 kept on actively. After three minutes No. 4 begins: Nos. 3 and 5 are blank.

We have tried to get a graphic representation of this phenomenon. A keyboard with five keys was connected each with a signal magnet arranged to write on a drum. Five glomeruli in a field were chosen and a key assigned to each. Discontinuance of flow was registered by pressing the key and keeping down till flow resumed. The recorder also noted on the drum obvious variations in rapidity of flow which could not be designated as complete cessation or resumption. Charts were then made of these records.

Study of these charts forced the conclusion that while at times there are interruptions common to all, in the main the circulatory activity of one is independent of others: and the inference is drawn that a local regulatory mechanism must exist analogous to that shown by Krogh to exist in muscles.

Preliminary attempts to gain deeper insight into the circumstances of this phenomenon have been made. Not very much can safely be stated at present. We are sure that the phenomenon of intermittence persists after complete destruction of the whole central nervous system—brain and cord. There is evidence that intermittence of the glomerular circulation is commonly associated with simultaneous and synchronous intermittence of the afferent vessel. In this connection it is very striking that when flow stops abruptly in a single active glomerulus corpuscles do not remain stagnant in its capillaries: they may remain for an instant then they fade out of view and the whole glomerulus may become invisible. This must mean that the capillaries of the glomerulus possess power of independent contraction, capable of

emptying their lumina after blood has ceased to flow. This statement must be held as applicable to the afferent and efferent vessel, since they as well as the glomeruli are emptied when blood flow stops. Dr. Schmidt has made one observation which we hope to repeat: in one instance capillary flow in the glomerulus ceased abruptly, and blood cells disappeared from it; but the afferent vessel remained full of blood, the corpuscles oscillating back and forth at the entrance of the glomerulus until presently the glomerular capillaries opened and flow through the whole structure resumed.

This emptying of the capillaries after cessation of flow—indicating, as we believe, independence of contractibility of their walls—is much less marked or may be absent in the dilated sluggishly flowing capillaries of some of the glomeruli to which reference has been made. These are apt to remain engorged with cells when flow ceases. We take this to mean that there are normal differences in tonus and normal variations in tonus.

We do not yet know what the nature of the influence which regulates this tonus is.

Making the assumption that these observations are applicable to the mammalian kidney, they give me a conception of glomerular circulation different from that which I had previously held. Instead of a uniform circulation of blood through all the glomeruli, varying with general and renal blood pressure, we conceive of a circulation, restricted under conditions of moderate blood flow to only a fraction of the glomeruli; and instead of equal circulation through all of the capillaries of a single glomerulus we conceive of the possibility of restriction of flow through a fraction of the available pathway. This restriction in number of functioning glomeruli and in patent capillary loops may be brought about by general influences (circulatory and nervous) brought to bear from outside the kidney and unequally effective in different units of the kidney through anatomical differences, such as length of vessel; in addition we think of the restriction as due to a local, peripheral control of contractile power, not only of afferent and efferent vessels but of the intervening capillaries as well. The phenomenon of intermittence permits us to

think of alternating rest and activity of glomerular structures and prevention of damage such as would conceivably result from prolonged interruption of blood flow.

The phrases "dilatation of kidney vessels" and "constriction of kidney vessels" come to mean not only the increase and decrease in volume and rate of a stream already flowing but also the increase and decrease in actual number of functioning glomeruli and of open glomerular capillaries. The possibilities in the direction of increase or restriction of filtering surface become more impressive.

On this basis it is not difficult to understand how relatively enormous changes can take place in glomerular blood flow without correspondingly great changes in the size of the kidney as registered by the oncometer. For obviously the capsule does not collapse when flow through the tuft ceases. It is easy to understand and to accept such puzzling experiments as those of Lœwi—in which the ability of blood flow to increase under influence of caffeine in a kidney imbedded in plaster of paris was demonstrated.

It becomes easier to understand how a kidney might eliminate from blood of the same composition and in equal spaces of time urines of widely different composition: for a urine issuing as the result of highly active blood flow and high glomerular pressure in a smaller number of glomeruli must be different from that which issues as the result of slower blood flow and lower glomerular pressure from a larger number of glomeruli. The resorptive powers of the tubules would be effective to different degrees.

The difficulty of injecting the glomeruli uniformly even in fresh kidneys is comprehensible; as is also the lack of uniformity among the glomeruli in the action of circulating toxic substances.

A lead may be given concerning the causation of albuminuria under conditions not far removed from the physiological: it is a very old observation that complete arterial interruption of the circulation in the kidney for a short time is followed by albuminuria. If intermittence of glomerular flow is a normal phenomenon, it would appear that albuminuria might occur if, for any

reason, the duration of the normal intermittent cessation of flow increased.

If you will permit me I will give the briefest resumé of the chief points which we have attempted to present:—

1. New evidence has been secured that increment of blood pressure, uncomplicated by increment in velocity or volume of blood flow in the kidney increases urine formation. This is regarded as added support of the filtration hypothesis.

2. Evidence has been secured indicating that some of the most weighty objections to the filtration hypothesis can be reasonably explained in a manner consistent with it.

3. Indications have been shown that nervous stimuli and chemical substances may exert different degrees of effective influence upon the afferent and efferent vessels of the glomerulus, and that this may be a factor in that automatic regulatory control of glomerular filtration which is responsible in part for the maintenance of constancy of blood composition.

4. And finally a new description of the mode of circulation through the glomerular vessels has been presented which, when verified and extended, we hope will be of service in the study of the normal and pathological physiology of the kidney.

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TYPHUS AND RICKETTSIA*

DR. S. B. WOLBACH

Associate Professor of Pathology and Bacteriology, Harvard University

MY TASK this evening is a double one, to give you an outline of recently acquired knowledge of typhus as a disease and to place before you the present status of a group of micro-organisms, as yet poorly defined and insufficiently studied—the "Rickettsia" in which we find the most generally accepted cause of the disease under consideration.

The original work included in this lecture was done jointly with Professor John L. Todd of Montreal and Doctor F. W. Palfrey of Boston, and represents in part the results obtained by the Typhus Research Committee of the League of Red Cross Societies to Poland.* The origin of this Commission was the idea of Doctor R. P. Strong, at that time Medical Director of the League of Red Cross Societies.

Up to the time of our departure we had access to very few of the papers published in Germany during the war. Abstracts in English and French periodicals indicated that much excellent work had been done upon the pathology of typhus and the organisms associated with the transmission of the disease by lice—the latter pointing strongly to the probability of Rickettsia being the cause of typhus.

Although our work in Poland was planned wholly independently by Doctor Todd and myself along lines which were the direct outcome of previous work with other diseases, we find, now that it is finished, that it proves to be in the main, a carefully conducted control of the work of many widely separated investigators.

Nicolle, Comte and Conseil, in 1909, were the first to transmit

* Delivered March 12, 1921.

* Other members of the Commission were A. Bacot, M. C. McIver, James Denton, Henry Pinkerton, F. A. Hardy.

typhus to animals. They not only succeeded in infecting monkeys, but were able to transmit the disease from monkey to monkey by means of louse feeding experiments. Later in the same year Anderson and Goldberger confirmed the susceptibility of the monkey to Mexican typhus, and in 1910 that brilliant worker, Ricketts, and his associate, Wilder, confirmed both the susceptibility of the monkey to Mexican typhus and the possibility of transmission by the louse. Ricketts and Wilder also described in the blood of patients and in lice minute bacillus-like micro-organisms, which we now call Rickettsia. Other confirmatory work on the transmission to monkeys was done by Gaviño and Girard in Mexico.

The transmission of typhus to guinea-pigs by Nicolle, Conseil and Conor in 1911 was a great step forward. It presents another example of the value of repeated and painstaking trials in the face of initial negatively interpreted results. Nicolle and his associates showed also that the virus could be indefinitely maintained in guinea-pigs and that they were on the whole more susceptible than the lower monkeys available for laboratory purposes.

Hegler and von Prowazek, in 1913, saw bodies in polymorphonuclear leucocytes of typhus patients which they believed were micro-organisms, and in one instance, in smears of a louse, small paired coccus-like micro-organisms described by them so meagerly as to leave one in doubt as to the value of their observations.

Sergent, Foley and Vialette, in 1914, in a much more extensive study of lice from typhus cases, reported minute "coccobacilli" not found in thousands of control lice taken from normal persons. They also, in 1914, infected three human volunteers with typhus by means of lice, one by louse feeding, one by subcutaneous injection of louse emulsion and one by scarification with crushed eggs of infected lice.

Da Rocha-Lima, an associate of Prowazek, in later work upon typhus in 1916 described in detail the minute micro-organisms in typhus lice, and laid emphasis upon their intra-cellular situation in the epithelium of the louse's alimentary tract. He noted their occurrence in enormous numbers. Both he and Prowazek

became infected with typhus, presumably from dissecting lice, and von Prowazek died. Ricketts' fatal infection also, according to his Mexican friends, was through his experimental lice.

The name Rickettsia prowazeki was given by da Rocha-Lima to those minute micro-organisms in honor of these two unfortunate investigators, and from then on we find in the literature evidence for and against the etiological significance of Rickettsia in typhus, a similar problem in regard to trench fever and Rickettsia, and the recording of Rickettsia in lice from normal persons and in other insects than lice.

In 1914 Frænkel called attention to a specific lesion of the blood vessels of the skin in typhus; and a number of other German pathologists during the war made pathological studies confirming and extending Frænkel's findings, notably Aschoff, von Chiari, Jaffé, Kurt Nicoll, Ceelen and Spielmeyer. Ceelen, in 1916, noted lesions associated with blood vessels in the central nervous system in man analogous to the lesions in the skin. Von Prowazek, in the same year, described identical brain lesions in monkeys, and Ceelen, in 1917, the same lesions in the brains of guinea-pigs.

My own work on Rocky Mountain spotted fever between 1916 and 1919 had convinced me, just as Ricketts was convinced by his work, that this disease and typhus had many features in common. The inability to cultivate the rickettsia-like micro-organisms of Rocky Mountain spotted fever, necessitated a series of experiments which proved the specificity of the micro-organism which I named *Dermacentroxenus rickettsi*. With the agreement of Professor Todd, our work upon typhus was outlined upon the spotted fever work. Our program was not completely carried out owing to unavoidable delays in getting down to work and to the greater difficulties of working with lice as compared with ticks—chiefly in regard to their feeding habits.

Similarities between Rickettsia and Dermacentroxenus and between the pathological reactions of the two diseases in man and animals deserve some attention on this occasion.

In view of the large variety of micro-organisms cultivated from typhus and the non-conclusive evidence to be expected from immunological experiments, we placed greatest value in preliminary steps upon other procedures than cultivation experiments.

Our work was formulated to answer the following questions:

1. What micro-organisms are acquired by lice nurtured upon typhus patients?

2. Can any micro-organism be shown to be specific for lice nurtured upon typhus patients?

3. Can it be shown by animal experiments that any micro-organism is inseparable from, and therefore probably identical with the virus of typhus?

4. What is the distinctive pathology of typhus?

5. What micro-organisms can be demonstrated in the lesions of typhus?

The louse work required not only "clean" lice but lice controlled from time to time in regard to their freedom from micro-organisms.

It was also necessary to ascertain the types of micro-organisms present in lice collected from presumably healthy individuals in the region from which our patients were obtained, and in the pursuit of this material through the infection of Mr. Bacot we obtained valuable information about the etiology of Trench fever.

Before proceeding to the final question of etiology and nature of typhus, a brief review of the subject of Rickettsia is desirable.

The rickettsias of greatest interest are those found in lice in connection with typhus and trench fever and in lice presumably free from any disease virus. They have also been found in other "insects" which I shall take up later.

A satisfactory definition of Rickettsia is at present not possible, so I shall endeavor to mention the properties in common of the thirteen or fourteen micro-organisms so far described under this name.

Morphology:—Bacterium-like on the whole. They are smaller than bacteria and occur characteristically in pairs. Large forms, bacillary and filamentous, have been described in connection with two carefully studied rickettsias and it seems probable that a simple cycle or sequence in morphological development is a characteristic of the pathogenic forms.

Staining Reactions:—Difficulty of staining with the common staining solutions used for bacteria is a striking feature, as well as the failure to retain the stain by Gram's method. The only

satisfactory staining methods are the modifications of Romanowsky's method and the most satisfactory is Giemsa's solution.

Motility:—All are non-motile (but in view of a possible development cycle, a motile stage may yet be shown to exist).

Cultivation:—So far all have resisted cultivation with the exception of the rickettsia from the sheep "louse" which grows on a relatively simple glucose blood agar medium.

Resistance to Physical and Chemical Agents:—Not enough work has been done to generalize. The viruses of typhus and Rocky Mountain spotted fever are extremely susceptible to heat, drying and chemical agents. On the other hand, the virus of trench fever resists 80° C. of dry heat for twenty minutes and drying for many months.

Host Specificity:—All rickettsias have an insect host which in the case of the pathogenic ones are the vectors. All are highly specific for their insect host while the pathogenic ones may infect widely separated mammals.

Hereditary Transmission:—In every instance where careful study has been made it has been found—with the exception of the rickettsia of typhus—that the organisms pass down through successive generations, in the eggs. Rocha-Lima has offered some evidence that this is also true of *Rickettsia prowazeki,* and Sergent, Foley and Vialette, 1914 (quoted by Nuttall, Parasitology, Vol. 10) accidentally communicated typhus to a monkey and a man with the offspring of lice which were supposed to be infected only with relapsing fever.

Classification:—Is of course impossible, and it is probable that we have already included under Rickettsia a number of very different micro-organisms. The rickettsia of the sheep "louse" has little to distinguish it from bacterium, while I believe the rickettsia of typhus has a number of peculiarities which necessitates its separation at present. The rickettsia-like cause of Rocky Mountain spotted fever which I prefer for the present to consider under a distinctive name, while resembling in many ways *Rickettsia prowazeki,* is very unlike the morphologically simple rickettsia of trench fever.

The following table indicates the wide distribution of "Rickettsia" in "insects" and one important generalization

which I believe to be warranted in view of their great specificity for their insect hosts and hereditary transmission is that they are forms of micro-organisms primarily adapted to insect tissues

with occasional representatives pathogenic for mammals. It must be kept in mind that the grouping of these micro-organisms under "Rickettsia" can only be tentative with the meagre data so far determined.

The following data concerning the Rickettsia in the preceding table are available.

Rickettsia mélophagia:—This micro-organism was discovered by Nöller in 1917 while studying flagellates of the sheep louse or tick. He succeeded in cultivating it upon a glucose blood agar medium. Jungmann in 1918 confirmed Nöller's work, including the cultivation, and determined that the infection of the insect host is hereditary. *Rickettsia melophagi* is not pathogenic, it occurs characteristically upon the cuticular surface of the epithelium of the sheep louse's stomach, but may invade the cells and in morphology it corresponds to the small or coccoid forms of *R. pediculi* and *R. prowazeki;* it is not pleomorphic.

The *unnamed Rickettsia* from the dust louse, Psocus, Sikora, 1918, 1920, is of course not associated with any mammalian host. It is transmitted hereditarily, lives wholly extracellularly in stomach of its host, and is non-pathogenic. Sikora was unable to infect Pediculus with this Rickettsia.

Rickettsia pediculi, Rickettsia quintana and *Rickettsia wolhynica* are morphologically identical and in all probability are identical (Wolbach and Todd, 1920), (Bacot, 1921). They are on the whole easier to stain than *Rickettsia prowazeki,* and are much more uniform in morphology. They are slightly plumper and more definitely oval than *Rickettsia prowazeki.* They occur characteristically extracellularly in the louse's stomach and adhere to the cuticular border of the stomach epithelium in a striking manner. Sikora and others maintain that exceptionally *Rickettsia pediculi* invades the epithelial cells of the louse's stomach, but we cannot confirm this statement. It is transmitted hereditarily in the louse. The virus of trench fever (and therefore *Rickettsia pediculi,* if we are correct in our conclusions) resists a dry heat of 80° C. for twenty minutes and ordinary desication in sunlight for long periods (four months) in contrast to the viruses of typhus and Rocky Mountain spotted fever.

Rickettsia prowazeki:—Is strikingly pleomorphic, multiplies exclusively within cells in the louse and is very susceptible to

drying and heat. Da Rocha-Lima has produced some evidence that in the louse it is transmitted hereditarily.

Rickettsia rocha-lima? Weigl in Warsaw in 1920 showed us preparations of lice containing intracellular pleomorphic Rickettsia indistinguishable by us from *Rickettsia prowazeki.* According to Weigl this is a non-pathogenic rickettsia infecting man and was acquired by lice fed upon himself and upon members of Denekin's army. We are not convinced that Weigl was dealing with a rickettsia other than *Rickettsia prowazeki.*

Rickettsia lectularius, Arkwright, Atkin and Bacot, 1921, is an extremely interesting micro-organism, morphologically very similar to *Rickettsia prowazeki* in pleomorphism and staining. It is non-pathogenic and is apparently widely distributed in bed-bugs in England and Europe. It multiplies exclusively intracellularly in various organs of the bed-bug and is transmitted hereditarily. Arkwright, Atkin and Bacot describe a morphological cycle or sequence of forms, similar to that of *Rickettsia prowazeki* and *Dermacentroxenus rickettsi.*

The *unnamed Rickettsia from culex pipiens* discovered by Nöller and referred to by Sikora, 1920, occur extracellularly in the mosquito. No further data are furnished.

Rickettsia ctenocephali, Sikora, 1918, is a non-pathogenic micro-organism exhibiting large and small forms, but not as pleomorphic as *Rickettsia prowazeki* and *Rickettsia lectularius.* It occurs in the coelum of the cat flea and is transmitted hereditarily.

The *unnamed Rickettsia from the mouse flea* was briefly mentioned by Sikora in 1918. It occurs intracellularly in the Malphigian tubules.

The *unnamed Rickettsia from the bird mite* is another intracellular representative discovered by Nöller and mentioned by Sikora, 1920.

The *Rickettsia in the Kedani mite* is highly questionable. Sikora, 1920, mentions it as a recently discovered cause of Tsutsugamushi disease, information of which came by word of mouth.

Dermacentroxenus rickettsi, the cause of Rocky Mountain spotted fever, has been included among Rickettsia by a number of authors and I have therefore included it in the above table.

A comparison with *Rickettsia prowazeki* while showing a number of common features, brings to light many differences in morphology and in behavior in the insect vector. Dermacentroxenus is less bacterium-like than any of the Rickettsias and in multiplicative form always shows red and blue staining materials. It does not appear in thread-like or filamentous forms as does *Rickettsia prowazeki.*

In the louse *Rickettsia prowazeki* continues to multiply indefinitely in the stomach epithelium, eventually causing the death of the louse through suspension of digestion. Dermacentroxenus, however, after a stage of active multiplication, largely *intranuclear,* floods all the tissues of the tick and then diminishes in number, leaving behind in certain tissues, including the salivary gland, forms which are different from the multiplicative forms and which I regard as in a resistant stage.

For the present I prefer to keep separate Dermacentroxenus —a parasite in Arachnida—from the Rickettsia which are parasites in Insecta.

Cross immunity experiments now in progress show that guinea-pigs which have recovered from typhus respond differently from normal guinea-pigs to inoculation with Rocky Mountain spotted fever. While all the typhus immune guinea-pigs developed spotted fever, they all showed a lengthened incubation period, and lower temperatures. The mortality was also strikingly reduced by about 50 per cent.

The Rickettsia that concern us most are those in lice. Early control work by Brumpt and Strong, apparently based wholly upon the examination of smear preparations, showed the presence of rickettsia in lice from presumably disease-free persons in France. Da Rocha-Lima, in 1916, showed that there were two types of rickettsia in lice, one extra-cellular, which multiplied wholly outside of the epithelial cells of the gut in the lumen and upon or in the cuticular border of the cells, and one associated with typhus which multiplied exclusively within the epithelial

cells of the louse's gut. The former he named *Rickettsia pediculi* and he believed it to be a non-pathogenic micro-organism confined to the louse. The latter is *Rickettsia prowazeki.* In no control work has it been shown that intracellular rickettsia occur in lice from a certainly typhus free-population, although both Rocha-Lima and Tœpfer state that very rarely *Rickettsia pediculi* may invade the cells. Todd and I, in view of the heavy typhus infestation of the countries in which this work was done, regard these observations as open to strong doubt. On the other hand, since the association of Rickettsia with trench fever has been given etiological significance by Toepfer, 1916, Munk and da Rocha-Lima, 1917, Arkwright and Bacot, 1919, Byam, 1919, and since the rickettsia observed by these authors are of the extra-cellular proliferating type and indistinguishable from *Rickettsia pediculi* of da Rocha-Lima, the question of deciding the specificity of Rickettsia for trench fever is a most difficult one. The query is:—are *Rickettsia quintana* (*wolhynica*) and *Rickettsia pediculi identical?* If so, is this Rickettsia the cause of trench fever?

Our control work with lice in Warsaw demonstrated the common occurrence of exclusively extra-cellular rickettsia in lice collected at a public bath-house. Mr. Bacot, of our commission, who collected and worked with these lice between March 31 and April 5th, developed on April 17th a sharp febrile attack and subsequently underwent a course of illness corresponding objectively and subjectively with trench fever. He was carefully studied by our own physician, Doctor Palfrey, and by Doctor Kruger of the American Red Cross. Mr. Bacot, during this period, was feeding upon his person a stock of lice brought from England, which were known to be free from rickettsia for a period of over two years before our work and which were carefully controlled by us just prior to Mr. Bacot's illness.

On April 27th Rickettsia began to appear in Mr Bacot's stock lice. They shortly appeared in enormous numbers and study of the lice by serial sections showed that they were always extra-cellular. Now follows what we regard as the most important observation of all—that Mr. Bacot (*Brit. Med. Jour.,* 1921, Jan. 29, p. 156) continued to infect clean stock lice fed upon his person

with Rickettsia long after his recovery, as late as September, four months after the attack and three months after the disappearance of all symptoms. We have here strong presumptive evidence that Mr. Bacot acquired his infection from the Warsaw lice and that the Rickettsia transmitted by him to his own stock of lice were identical with those in the Warsaw lice. We believe that these experiences constitute strong evidence for the identity of *Rickettsia pediculi* and *Rickettsia quintana* (*or wolhynica*) as well as for the eiological relationship of Rickettsia to trench fever. They predicate of course that the mass of population in Central Europe is immune to trench fever, and tolerant of *Rickettsia pediculi* infection.

For the present time then we must assume that there is but one type of extra-cellular rickettsia in human lice,*Rickettsia pediculi* (*Rickettsia quintana, Rickettsia wolhynica*).

Certain observations which are not reconcilable with the acceptance of Rickettsia as the cause of trench fever have been made by Brumpt and Strong. The former not only found Rickettsia in lice from presumably healthy prisoners of war, but failed to experience any ill effects from nurturing these lice upon himself. Strong also fed Rickettsia containing lice collected from healthy individuals upon other healthy individuals without observing any ill effects.

According to Strong's experiments, the virus of trench fever is not transmitted by infective lice to their ova, while according to a number of observers, including Bacot, *Rickettsia pediculi* are found in the ova; a discrepancy which would indicate that the virus of trench fever and Rickettsia are separable. The positive filtration experiments of Strong with trench fever virus may also be regarded as evidence contrary to acceptance of Rickettsia as the cause of trench fever.

Our own work with Rickettsia from typhus cases was done with lice brought by Doctor Todd from Canada and by myself from Boston, and fed during the duration of the research upon ourselves. They were repeatedly examined before, during and at the conclusion of the research and remained free from infection of any sort. Some of them were fed for short periods on other

members of the commission so that we know that they harbored no virus as well as no demonstrable micro-organisms.

What did these lice acquire in the way of micro-organisms while feeding upon typhus cases? The answer is *Rickettsia prowazeki!* We fed our lice in boxes and each box was usually placed on several cases. From twenty to forty lice were used in each box and fifty-two boxes out of sixty-five were successfully put through outlined programs. Lice in twenty-five of these boxes became infected, but when we finally recognized the conditions favorable for infection of the lice, i. e., temperature between feedings; stage of the disease and duration of the experiment, we were able to secure infection of lice with Rickettsia in each of the last thirteen consecutive feeding experiments. The intracellular location of the Rickettsia was demonstrated in lice from every box by serial sections, and the pleomorphism which has distinguished *Rickettsia prowazeki* from *Rickettsia pediculi* in our experience was constant in the smear preparations.

We found, however, that the lice did not become uniformly infected in positive boxes, and that frequently a high proportion remained uninfected with Rickettsia and the question arose;— is it possible to have the virus present without demonstrable micro-organisms This we attempted to answer by guinea-pig inoculations with the alimentary tracts of lice taken at random from lots which had been given ample opportunity to become infected. The injections were always made intra-peritoneally and at the time of dissection of each louse a preparation was made for microscopical search for Rickettsia. All remaining lice from the same lots were examined by smear preparations and by serial sections in order to determine the percentage which contained Rickettsia. The results of the guinea-pig inoculations were judged by a characteristic temperature reaction following a suitable incubation period, and were in nearly every instance controlled at the conclusion of the experiment, either by the injection of blood from an early typhus case or in the case of positive temperature reactions, by histological examination of the brain and by inoculation of other fresh guinea-pigs. The human blood used in testing the immunity of the guinea-pigs at the

conclusion of the experiments was proved to be infective for fresh normal guinea-pigs.

By these experiments we proved that of a number of lice fed in the same box, some would become infected with the virus of typhus, others not, and therefore, that uniform infection with Rickettsia was not a requirement in a chain of evidence. Although our experiments were fewer in number than we should have done had more guinea-pigs been available, the results, based upon forty-two guinea-pigs inoculated with gut emulsions of lice from ten boxes brought to light other important facts.

Of the forty guinea-pigs thirteen developed typhus. All of these thirteen guinea-pigs were inoculated with lice from four boxes, some members of which from each were infected with Rickettsia. Of twenty guinea-pigs inoculated with lice from the other six rickettsia free boxes none developed typhus, though two died within a few days of pneumonia. Rickettsia were found in the smear preparations of nine lice used to infect the thirteen guinea-pigs, so in but four instances did we fail to find Rickettsia in the preparations from lice that did convey typhus. Since we have proved by the study of serial sections of lice that but one cell of the stomach epithelium may be infected with Rickettsia at the conclusion of a feeding experiment upon typhus patients, it is obvious that the examination of a small portion of the emulsion used for injection is not an adequate test for the presence of Rickettsia in infective lice. In no instance did lice containing Rickettsia fail to infect guinea-pigs. On the other hand, in seven lice from *infected* boxes which failed to convey typhus to guinea-pigs, no Rickettsia were found. We are inclined toward the conclusion—from the above experiments that the virus of typhus in the louse is inseparable from Rickettsia.

In six of the fifty-two boxes we found a few lice doubly infected, with *Rickettsia prowazeki* and *Rickettsia pediculi.* These six boxes were all fed at the same period—about the middle of our research—and the source of infection with *Rickettsia pediculi* was with considerable certainty traced to three of several patients on whom these boxes were fed. The occasional occurrence of *Rickettsia pediculi* was anticipated by us because of our experi-

ence with the Polish lice from which Mr. Bacot became infected.

The study of *Rickettsia prowazeki* is not completed, but I shall give an account of what information we have. The Rickettsia of typhus literature is a small bacterium-like micro-organism, ovoid or elliptical in shape, usually occurring in pairs. Short and long rods with polar bodies and coccoid bodies in chains have been described. The ovoid coccoid form in pairs is usually regarded as the type form. The two elements composing the pairs stain deeply with Giemsa's stain, taking a red coloration while the material between the two stains pale bluish. Where the organism occurs singly there is often a zone of pale blue material surrounding or tapering from the deeply staining red ovoid body. The minute paired forms, while composed usually of ovoid elements, are often composed of two pyriform elements joined at their narrow extremities lying in a straight line or forming an obtuse angle. These pyriform elements stain blue and contain in their distal extremities red stained, round, ovoid or ellipsoidal bodies. They seem to be a variation or possibly a divisional stage of the blue staining rod form with polar bodies described below.

The minute cocoid and paired coccoid forms were invariably present in greater or less numbers in all our preparations from Rickettsia infected lice.

Measurements by us from negatives of photomicrographs made accurately at 2000 diameters and read under low magnification with a micrometre ocular calibrated so as to make ten divisions of the scale equal one millimetre, give the following dimensions. The smallest single elements range from 0.25μ by 0.4μ to 0.3μ by 0.45μ. The paired forms range from 0.25μ by 0.7μ to 0.3μ by 1.1μ. (The above method of measuring micro-organisms is probably accurate to 0.05μ).

These measurements correspond closely to those of da Rocha-Lima who gives 0.3μ by 0.4μ for single elements and 0.3μ by 0.9μ for the paired forms.

In all smears, in addition to the small forms described above, we have noted the presence of small numbers of slightly larger, more deeply staining and more uniformly shaped paired coccoid

bodies, somewhat lanceolate in shape and devoid of bluish staining intermediate substance. These forms can be recognized in sections of lice and are the forms most easily demonstrable in human tissues.

In the systematic examination of one hundred and eighteen smears containing *Rickettsia prowazeki,* the rod-like forms mentioned by da Rocha-Lima with deeply stained polar granules, were seen frequently in large numbers and almost invariably in small numbers. They are proportionately most numerous in sparsely infected lice and stain best when embedded in fragments of cytoplasm. The polar granules stain deep red, the body of the rod is light clear blue, their dimensions range from 0.25μ to 0.35μ in width to 1μ to 2.5μ in length. Other palely staining rods, much swollen in the central portion and capped at each end with a biscuit-shaped red staining body, occur in the presence of the bacillary forms and probably represent degeneration or involution forms. A third form, which has been described previously only by Otto and Dietrich, has been seen often in smears by us, and is associated with early infection of the louse or of individual cells in the louse. This is a filamentous form and its association with early infection of cells is based upon the study of sections of infected lice.

For a considerable period in our work we avoided decision upon delicate filamentous forms which appeared only in lice fed upon typhus patients and never in the control lice. Constant association of these forms with the minute forms in the same lice or in other lice from the same boxes and the failure to find them in smears from any louse which, though fed upon typhus cases, did not produce typhus when injected into a guinea-pig, compelled us to accept them as a form of *Rickettsia prowazeki.*

These filamentous or thread-like forms in smear preparations are usually curved, sometimes sharply flexed in one or several places. In width they range from 0.3μ to 0.4μ and in length are often extraordinary, 10μ to 40μ or 50μ. The threads stain blue and the outlines seem unbroken though varying slightly in width in the same filament. Within the blue stained filaments are red stained bodies in pairs and chains corresponding in

dimensions to the free lying Rickettsia bodies. Some of the thread forms stain homogenously—pale blue. Within a single filament the arrangement of the red stained bodies suggest the division of the whole into any one of the previously described forms, coccoid bodies singly or in pairs and the thick or slender bi-polar bacillary or rod forms. In occasional preparations we can identify portions of crushed epithelial cells from the louse gut filled with enormous numbers of filamentous, rod and coccoid forms with apparent stages in the formation of the two latter forms from the former.

The early occurrence of these filamentous forms is borne out by finding them in sections of lice lying curled within non-swollen cells of the mid-gut at a time when very few cells are infected with the coccoid Rickettsia. Similar bacillary and threadlike or filamentous forms have been described by Arkwright, Atkins and Bacot as a part of the developmental cycle of a Rickettsia-like (*Rickettsia lectularius*) parasite of the bed-bug. These authors suggest that the small Rickettsia (lectularius) bodies develop through the bacillary stage into filaments while others continue to multiply by simple fission. The filamentous forms finally break up into the minute Rickettsia bodies. An intracellular development of minute forms also leads to the formation of larger lanceolate paired forms from which bacillary and filamentous forms develop.

The demonstration of Rickettsia in man and experimental animals is much more difficult than in lice. We have not been able to find them free in the blood plasma as described by Ricketts, nor are we prepared to accept von Prowazek's conclusion that granules seen by him in leucocytes are Rickettsia; they may be micro-organisms, but we cannot prove that they are different from granules seen in leucocytes from non-typhus cases.

Before going further into this problem in our chain of evidence it is advisable to consider in some detail the pathology of typhus.

Ricketts, as others before him, classed typhus with plague as a hemorrhagic septicæmia. The German investigators during the war described the essential lesions of the disease in connection

with blood vessels, and I now venture to describe the disease as one of the blood vessels of the skin, musculature and central nervous system. It is a disease affecting primarily one tissue, the vascular endothelium, and is attended by marked proliferative reactions of this tissue.

It was part of our program to learn all we could about the disease process in typhus, because in tissue reactions we find evidence for classification or the grouping of diseases and from them may sometimes predict the probable nature of the exciting agent. Our knowledge of histo-pathology is now sufficiently complete to warrant the formulation of a few criteria for prediction. I was almost tempted to say laws—but I shall say *invariable histological sequences.*

In the infectious diseases a proliferative response means I believe the presence of the exciting agent within the affected cells; I need in this connection only to mention tuberculosis, leprosy, syphilis, the Leishmania infections, and finally Rocky Mountain spotted fever.

The lesions in typhus take origin in blood vessels, and while cell degenerations occur which lead to thrombus formation and hemorrhages, the initial reaction is in large degree proliferative. Within the lumina of blood vessels the evidence is complete in regard to the role of the endothelium, but there is also a marked proliferation of cells in the perivascular zones on the part of cells whose origin may be disputed. We believe them to be cells of endothelial origin, but we can avoid dispute by calling them macrophages. In the perivascular collections of cells there are of course many cells of other types, polymorphonuclear leucocytes and cells of the lymphocyte series.

The total volume of surface affected in typhus is very great, including as it does the vessels of the whole surface of the body, and the voluntary muscles. In the viscera minor involvement of capillaries and vessels of pre-capillary size are found in the heart, rarely in the lungs, in the kidneys and in the male genitalia. Lesions of the genitalia, however, in marked contrast to Rocky Mountain spotted fever, are not constant or striking. The central nervous system, again in complete contrast to Rocky Mountain

spotted fever, is the seat of extraordinary lesions. The lesions, while always associated with small blood vessels—capillaries and pre-capillaries—extend into the substance of the nerve tissue. They constitute one of the most interesting features in the pathology of typhus. They involve all portions of the central nervous system, but are most numerous in the medulla, mid-brain, pons and basal ganglia of the cerebrum. These nervous lesions, when fully developed, may reach the size of miliary tubercles, and are composed of endothelial and neuroglia cells, among which fibrils do not appear until late. It is the most striking of the proliferative reactions to the virus of typhus and it is not in any way to be considered merely as a perivascular reaction, because it is a true invasive lesion of the brain tissue. It has taken very careful study to arrive at the somewhat tentative conclusions that this proliferative reaction on the part of the neuroglia is always preceded by a lesion of a blood vessel. Much help has been obtained from brains of animals, as every stage in the development could be studied, and here again we have ascertained that the first response in the brain, as elsewhere, is a reaction of the vascular endothelium, evidenced by swelling, mitotic division, and thrombosis. We are of the opinion, which we cannot yet fully support by objective evidence, that the virus of typhus is taken up or enters the neuroglia cells, and is responsible for the continuation of the process. This is further borne out by the fact that occasionally guinea-pigs which recover from the acute disease sometimes after a considerable period of normal temperature, succumb to the nervous lesions, dying with symptoms very much like those of rabies. The test of this opinion will be furnished when we have demonstrated the presence or absence of the virus in the nervous tissue after a period of normal temperature. It seems also probable that the peculiar and characteristic perivascular lesions in the skin and elsewhere are brought about by the migration of endothelial cells carrying the parasite into the perivascular zone. We are fairly certain that we have demonstrated Rickettsia in such regions.

The pathology of typhus is so distinctive that a diagnosis may be made by histology, directly from excised skin of patients

or by the examination of the brains of inoculated guinea-pigs. In the experimental study of typhus we are firm in demanding histological control of experimental animals, whenever the presence of typhus is a requisite for drawing conclusions.

In typhus, as in Rocky Mountain spotted fever, we are presented with a puzzle in the escape of many vascular organs. We failed to find lesions specific of typhus in the thyroid, pancreas, adrenal glands, gastro-intestinal tract and liver. In the pituitary the glandular portion escapes lesions, while the nervous portion in a very high percentage of cases shows specific lesions. I only mention this as one of the unexplained features of the disease.

The pathology of typhus explains quite satisfactorily the symptomatology. It is not a septicæmia, but we have only to consider the tremendous area represented in the capillary and pre-capillary circulation of the skin and muscles to account for the severe toxic manifestations, while every phase of the rash may be shown to correspond with the type of damage done to blood vessels. The very peculiar extensive surface necrosis of the body, unlike the decubitus of other diseases, we have shown to be due to centripetal extension of thrombi, beginning in the skin. The symmetrical, so-called "gangrene" of extremities may possibly be due to involvement of nerves, and occasionally we have found lesions of blood vessels within nerve trunks. The nervous symptoms which are so prominent in typhus, excitability, delirium, coma, meningismus, trismus,, and cerea flexibilitas, are in all probability associated with the lesions of the central nervous system. Certainly of the cases studied by us clinically those which have shown the severest nervous symptoms have shown the most extensive pathology of the central nervous system. The motor symptoms are consistently to be co-ordinated with involvement of the cerebral cortex, and we are inclined to believe that the extensive involvement of the fourth ventricle, which is occasionally accompanied by capillary hemorrhages, may account for the vaso-motor collapse, which was occasionally seen in our series.

The last important link in our chain of evidence was the dem-

onstration of Rickettsia-bodies in human and animal lesions. This has been accomplished by means of the same technique employed in the study of Rocky Mountain spotted fever, with more difficulty, however, because of the smaller size and weaker affinity for stains. In typhus tissues two forms of Rickettsia-bodies can be found, a larger, more deeply staining paired form, usually lanceolate, and surrounded by a clear zone, and a smaller paired form, usually occurring in masses. Such findings have been constant in practically every post mortem obtained before the thirteenth day of the disease, in a fresh condition, a total of twenty-five. They have been found with regularity in skin excised from fifteen living patients. Actual proof that these bodies seen within endothelial cells are identical with those observed in the intestinal epithelium of lice is beyond our means at present. All we can say is that we are dealing with forms unquestionably parasitic in nature and consistent in morphology with Rickettsia.

This carries me through the main purposes of our work as permitted by the amount of time at my disposal. We have the constant association of a parasite in lice fed upon typhus cases, in lice known to be free from micro-organisms and carefully controlled, before, during and at the conclusion of the experiment. We have made experiments which prove that the presence of this parasite, *Rickettsia prowazeki,* is necessary for infectivity of the louse for guinea-pigs, and finally, we have demonstrated in tissues in the lesions of typhus a parasite morphologically consistent or identical with *Rickettsia prowazeki.*

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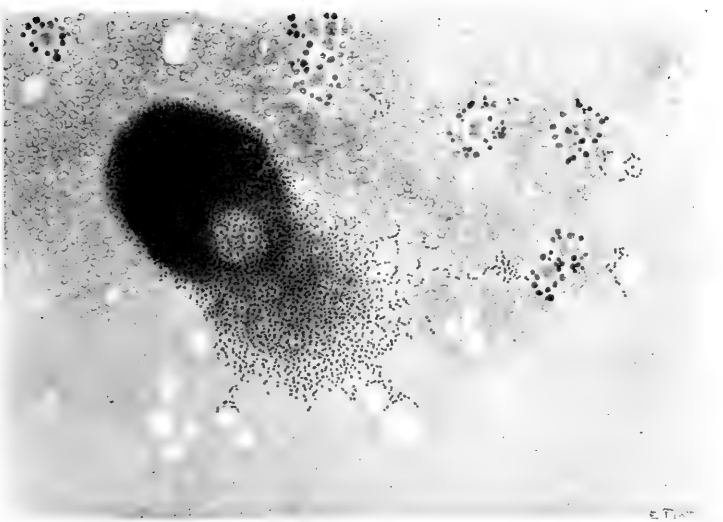

FIG. I.—Smear preparation, gut of louse infected with Rickettsia prowazeki. 1500 diameters.

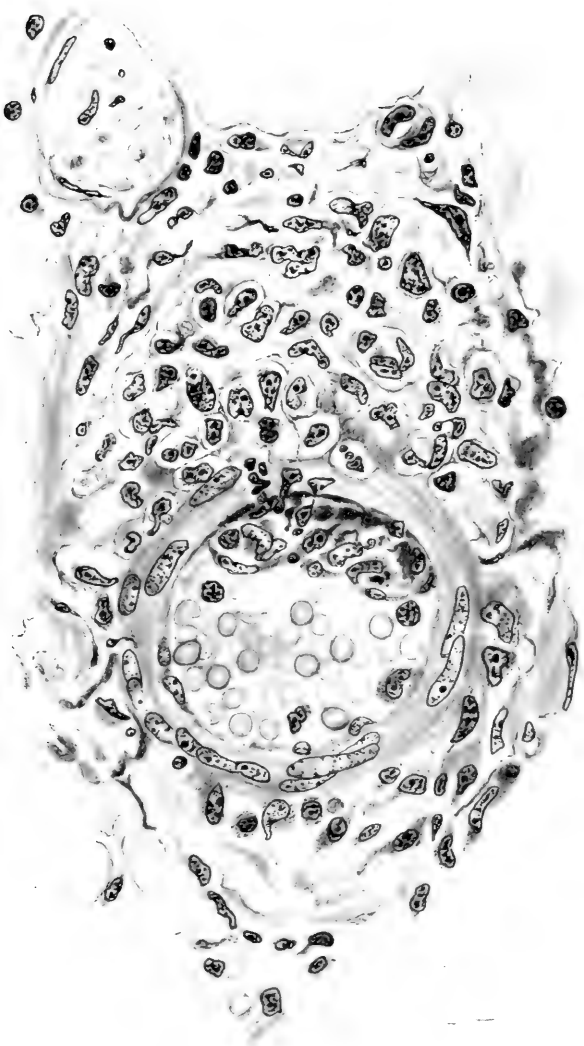

FIG. II.—Early typhus lesion in a human artery of the skin.

FIG. III.—Rickettsia prowazeki in endothelial cells of a capillary of the skin. Mexican Typhus. Human case.

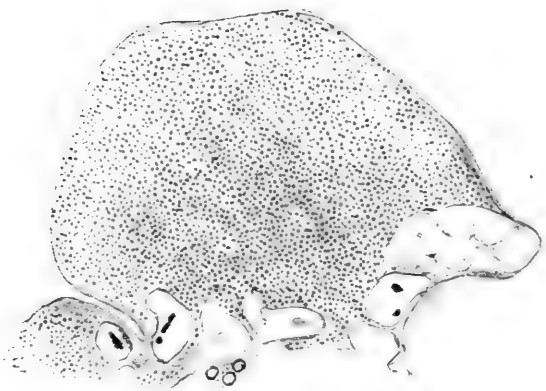

FIG. IV.—Cell distended with Rickettsia, from the stomach epithelium of an experimentally infected louse. The size of the Rickettsia is slightly exaggerated in relation to the magnification of the cell.

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CHEMICAL DYNAMICS OF MUSCLE*

DR. F. GOWLAND HOPKINS

Professor of Biochemistry, University of Cambridge.

THE task of the biochemist has scarcely begun when he has merely determined the nature of the substances which occur in living tissues. He must, if he will justify his calling, endeavor to define the part played by each one of these substances in those dynamic events which underlie the manifestation of life. He used, indeed, to be assured that this task was impossible because by the mere intrusion of his methods such events are annihilated. No student of biology dare, of course for the moment forget the peculiar instability of the materials with which he works. But the recent striking progress of Biochemistry has shown that the supposed predicament can, given sufficient ingenuity, be avoided.

In this lecture an account will be given of certain endeavors made to relate material changes with energy exchanges in the case of a tissue which offers certain special advantages for study. In a striated muscle we have an organ of which the normal function is at any time easily displayed and remains as a sufficient criterion of life. If, even when out of the body, a muscle on stimulation responds with a normal contraction we should strain our philosophy by denying that it is "alive." So long as it thus responds, even if it be with diminishing vigor, there is still something left for study of the arrangements which constitute the living condition. In the case of amphibian muscle which, as in other departments of physiology, has been much employed in the researches I am to describe, we have the additional advantage of dealing with a tissue which, given the right conditions—and of these an efficient oxygen supply is among the most important—yields the above criterion of life for days, and, at low temperatures, even for weeks after it has been removed from the body and deprived of a circulation. Hence in this connection, as in

* Delivered April 2, 1921.

others, its great convenience. Almost every fact that I am to mention, however, has been shown to apply to mammalian as well as to amphibian muscle.

Of the researches to be reviewed some have been long familiar; others are quite recent, and one or two have not yet been published. I would like you to understand, however, that you will be asked to follow one line of progress in particular, and the development of a consequent and particular point of view. Without neglecting any fundamental facts, which in my opinion militate against that point of view, I will take a straight path towards it, avoiding all collaterals, however interesting and important.

It is in connection with the functions of oxygen in living processes that the study of striated muscle displays its greatest interest. Till recently it had taught us most of what little we know about oxidation in animal tisues; at the moment it seems to be revealing quite unexpected aspects of these fundamental processes. Even since Lavoisier and Laplace made the great contribution to knowledge which more than any other has served to emphasize the unity of nature biologists have been trying to decide how precisely materials burn in the body. Needless to say no history of these efforts can be attempted here: but I will ask you to recall the development of one particular idea and to realize how potent has been its influence upon biological thought. I mean the conception that oxygen does not function in a living tissue immediately upon its arrival, but is first built up into an unstable complex which, only subsequently, when the tissue receives a stimulus, yields free energy by a sudden breakdown. This conception has led to, and is inseparably associated with, all those views which visualize life, as having its essential seat in living giant molecules, subject to continuous breakdown and reconstruction. Such views, held vaguely, or, as in the biogen hypothesis of Verworn and the side chain theory of Ehrlich, made highly objective, have greatly dominated thought.

It was in connection with muscle when in 1867 Hermann put forth his *inogen* hypothesis that in an elementary form they

arose. In my belief a fair consideration of the facts now known about the muscle is sufficient to prove them wrong..

You will of course remember that in Hermann's view the contraction of muscle follows upon the sudden, almost explosive, breakdown of a complex substance leading to the appearance of lactic acid and carbon dioxide. This unstable stuff is the *inogen*, the source of energy. At first, influenced by his belief that the processes of Rigor Mortis were in essence similar to those of a Contraction, Hermann taught that the protein myosin, which separates in a gelatinous form during rigor, was part of the *inogen*. It is sufficient, however, to remember that the essence of Hermann's teaching was that the production of carbon dioxide in muscle depends not upon the direct and contemporary oxidation of relatively simple compounds, but upon the transference of oxygen, previously combined in a complex molecule from less stable to more stable relations. Thus arose that conception of intramolecular oxygen which has given form to many biological speculations. Up to near the end of the last century the evidence seemed to justify it fully enough. Spallanzani, who seldom was in error, had shown even a century earlier, that living tissues could long survive and continue to yield carbonic acid without any supply of oxygen except such as had been previously available. Spallanzani's statements were in later years fully confirmed by others and Hermann made the evidence rather more definite in the case which especially interests us by showing that no trace of oxygen could be pumped out of a muscle which nevertheless could actively contract without an external oxygen supply, and at the same time produce carbon dioxide. Hermann's consequent views related in particular to the case of muscle, but as you will know Pflüger later on—(with vague speculations as to the respective nature of dead and living protein)—taught that all tissue respiration is based upon the activity of intramolecular oxygen.

Such views were almost unchallenged for thirty years and since I am now to speak of work done in Cambridge, England, it is of interest to point out that, in a certain form at least, they satisfied the critical mind of him who founded this Cambridge

school, as any who read the last edition of his famous text book will discover. This edition had not long left the press, however, when one of the last of the brilliant group of workers directly inspired by Michæl Foster, began some work which was to change the whole outlook.

In 1898 W. M. Fletcher[1] published an account of an observation which like many other observations of great importance was in a sense of a simple nature. The technique which made it reliable was not simple, however, and the value of the observation arose from its quantitive nature. Properly estimated it will, in my opinion, be found to have wholly removed the foundation of a belief which, as we have seen, had long dominated animal physiology. Excised surviving muscle gives out, it is true, a steady stream of carbon dioxide. It is clear, however, and it is assumed, implicitly if not explicitly, in all that has been attributed to Hermann's *inogen* that if this CO_2 arises from this hypothetical unstable source of energy, the amount should increase when the muscle passes from rest to activity. The breakdown of the *inogen,* which is *ex hypothesi,* the source of energy must surely be increased when the liberation of energy is increased. Therefore, since the *inogen* is also the source of the CO_2, a muscle, though wholly deprived of oxygen, must give out more CO_2 when it contracts than when it is resting. Fletcher showed that it did not.

The fact is fundamental. So long as a muscle remains in any sense normal, prolonged stimulation under anærobic conditions, fails to produce any effect upon its small but steady output of CO_2. Very different, as Fletcher further showed, is the case where a contemporary supply of oxygen is available. The output of CO_2 during rest is then greater and this output is at once increased when work is done. This difference between the chemical response to stimulation under anærobic and ærobic conditions, respectively, is again fundamental. There is no evidence for the breakdown of a previously constructed *inogen,* but there is, on the other hand, clear evidence that Contraction is associated with an increase in contemporary oxidations.

But what of that relatively small but steady evolution of

CO_2 which does, after all, occur anærobically, whether the muscle be active or at rest? It may be stated at once that it is not a product of metabolism at all. It is not physiological. When, indeed, we attempt later to picture the cycle of normal events we may frankly forget it. It is merely carbon dioxide liberated from alkaline carbonates in the muscle as a result of the steadily increasing acidity which, as we are to see, is characteristic of the anærobic conditions. To the best of my belief it was H. M. Vernon[2] who first suggested the possibility of such an origin: Hill afterwards referred to it, and later Fletcher[3] settled the matter by experiment.

Fletcher's early work provided further facts of significance. He fully confirmed the historical statements of Humboldt and later observations of Joteyko by showing that exposure of pure oxygen greatly delayed the onset of fatigue and of rigor mortis in excised muscle, but he went further and showed that a muscle which has lost the greater part of its irritability and is near to stiffening may be restored if exposed to pure oxygen.[4] From the facts which he made available Fletcher drew a conclusion which foreshadows an essential part of the story I hope to unfold. "It is suggested" he wrote in 1902, "that the hastening or rigor mortis and fatigue in a muscle from which oxygen is withheld is due to increased accumulation, under circumstances of deficient oxidation of the metabolic products within the muscle which are the potential precursors of carbonic acid;" while in the presence of oxygen "the dissociation processes alike of resting and active muscle, advancing slowly in the former, rapidly in the latter, result in the formation of free CO_2."

Since from the days of Berzelias lactic acid had been known as a constituent of muscle, and many observers, led by Dubois Raymond, had associated its production with activity and rigor, Fletcher was of course alive to the probability that this acid is among those precursors of CO_2 which accumulates anærobically; but he avoided at this time any dogmatic statement on the matter. The state of the literature as it then stood fully justified such caution.

Not long before, for instance, the statement had been made by

more than one observer that as a matter of fact there is no more lactic acid in a muscle in full rigor than in one perfectly fresh. Older views,—which had themselves never been supported by really quantitative work—were traversed, and the significance of lactic acid in muscle had become entirely obscure.

A quantitative study was clearly necessary for further progress and in 1907 it was my privilege to join forces with Fletcher in an attack upon the problem.[5] Although the results of our somewhat laborious research have failed to affect the teaching of some text books, we have the satisfaction of knowing that they have been the acknowledged point of departure for recent important studies.

We found that the confusion in the literature as to the quantitative relations of lactic acid in muscle were wholly due to faulty technique in dealing with the tissue itself. When the muscle is disintegrated as a preliminary to extraction for analytical purposes, the existing equilibrium is entirely upset. Interacting factors are brought into abnormal relations and the processes of change are greatly accelerated. A fresh muscle had been supposed to contain as much lactic acid as one in rigor simply because the acid had been produced in the former by the treatment which had preceded estimation. The biochemist had not sufficiently remembered the instability of his material. Fletcher and I, however, found it quite easy by means of a simple method, not only to avoid starting the changes which led to the formation of lactic acid but to arrest them at any point during their progress and thus to establish their time relations.

We were able to show that the accumulation of lactic acid in muscle occurs only in the conditions of anærobiosis. With a proper oxygen supply it fails to accumulate at all; though this is not to say that it fails to be produced. Its formation anærobically in a quiescent muscle shows no irregular relations: it is not, for instance, delayed until rigor appears, or is near. The accumulation starts from zero or from the minimal quantity present in fresh muscle and continues at a linear rate, equal amounts being produced in successive units of time. The reaction responsible for its appearance has a normal chemical temperature

cœfficient, at least between such temperatures as 10° to 20°C. At higher temperatures the effects of changes in the tissue structure become of influence and the process is accelerated so that at 40°C there is a very rapid rise to that "acid maximum" which Ranke described long ago. At still higher temperatures, and especially near 100°C, the process, like other biological processes, is arrested.

Stimulation increases the rate of production, as would be expected. We have indeed every reason to believe, and I shall later give recent evidence to support the belief, that in muscle the chemical processes of activity differ quantitatively only, and in no way qualitatively, from those that proceed during quiescence. If a muscle be tetanized to complete fatigue Fletcher and I found that the lactic acid produced always stopped short of that maximum which is found in Rigor Mortis or produced rapidly at 40°C. In the fatigue of tetanus the amount is about half that of Rigor (say 0.2 per cent as against 0.4)

Roughly to be classed as chemical stimuli, are the effects of certain volatile organic substances, such as chloroform, toluol, etc. When a muscle is exposed to the vapour of these a maximum yield of lactic acid is soon reached and a form of rigor is established; possibly because as solvents of lipoids these substances alter the permeability of membranes within the muscle structure.

The next point established by Fletcher and myself is of fundamental importance. If a muscle which, by exposure to anærobic conditions, has accumulated lactic acid, be placed in oxygen the acid is removed. The occurrence of this removal under the influence of oxygen is significant in all that follows. It has been fully confirmed by the later work of Parnas and Meyerhof.

The experimental findings so far discussed have removed all basis from the theory of intramolecular oxygen, and have shown that an excised muscle is quite able to obtain free energy from its stores of potential energy without the aid of oxygen. On the other hand while anærobic existence, passive or active, inevitably involves an accumulation of lactic acid in the muscle, sub-

sequent exposure to oxygen effects its removal. If, however, oxygen be available from the first it must be remembered that the acid does not accumulate at all.

There are therefore at this stage of the enquiry perhaps two possibilities to consider. The muscle when forced to dispense with oxygen may be supposed to derive its energy from potential stores by chemical steps differing entirely from those which occur under physiological conditions. If so, lactic acid may be an abnormal product playing no part in normal events. On this view the anærobic events are merely vicarious. But another possibility is that the normal cycle of events consists always of two phases separated in time: the first anærobic during which lactic acid is formed; the second ærobic during which it is removed. Now the conception of a respiratory sequence in which anærobic events precede and prepare the way for final oxidations has long been familiar to the minds of plant physiologists. Pfeffer for instance long ago spoke of the former as processes of intramolecular respiration, and looked upon them as necessary antecedents to subsequent oxidations. It is such a view that I propose to develop in connection with muscle, and I shall now proceed to give you further evidence in its favor. But the facts won in the study of muscle indicate that the influence of oxygen has in the case of animal tissues more complicated relations than those usually postulated for the case of plant tissues: relations which seem to me to have extraordinary interest.

At the close of our work upon lactic acid Fletcher and I were convinced that the influence of oxygen upon the activities of muscle is exerted after, rather than before, or during, the actual act of contraction and we were supported in this view by an observation previously made by Danilewski[6] who found that heat is given out by a contracting muscle after the actual contraction is over. The ordinary methods of chemical analysis however, seemed hardly capable of affording a final proof of this sequence. Clear evidence concerning the time relations of events could be best got from the study of a single contraction, a task impossible for the chemist.

At this stage, however, the Cambridge School of Physiology

gained an unusual advantage by recruiting, in the person of A. V. Hill; one who is at once an accomplished mathematician and a skilful experimentalist. Hill's qualifications have enabled him to advance very greatly the thermodynamics of muscle and to supply highly essential links in the chain of evidence which has led to the standpoint I am to advocate.

His studies have been made partly on the lines of microcalorimetry, but also, and more particularly, by the use of thermoelectric methods which he has greatly refined. A fundamental observation made early in Hill's researches puts upon a firm experimental basis the conclusion of Danilewski already quoted; namely, that the heat given out by an active muscle long outlasts the contraction itself.[7] But Hill's further time analysis of the thermal phenomena is so important to my thesis that it should be very fully grasped, at least in its essentials. The essentials are these. Directly associated with a contraction is a rapid evolution of heat, which occurs both under anærobic and ærobic conditions, and is, moreover, alike in its time relations and other characters, wholly unaffected by the presence or absence of oxygen.

Oxygen, however, has a noteworthy effect upon the sequel. In its absence the heat evolution just mentioned is quickly over, and is the only thermic change associated with the act of contraction. In its presence there is a further evolution of heat, subsequent to, and long outlasting, the act. These facts are clearly of great significance. The process which comes first must be anærobic; that which comes second can scarcely fail to involve an oxidation. We have here a proof of the suspected sequence of events, and data which strongly suggest that at the moment of contraction, even under conditions made normal by the available supply of oxygen, something is produced anærobically upon which oxygen subsequently acts. The chemical facts already discussed leave but little doubt that this substance is lactic acid, and evidence will be immediately given to show that the formation of the acid is as a matter of fact intimately associated with the process which gives rise to the early anærobic heat production. Later on we shall see that there are abundant reasons for associat-

ing the second oxidative heat production with the occurrence of its removal.

Already we may speak, at least provisionally, of two phases in the muscular act, separated in time: an anærobic phase of activity, or Fatigue Phase; and an ærobic phase, or Recovery Phase. It is convenient to make this distinction now. Further justification for it is inherent in all that follows.

The recovery phase must not be confused with the relaxation of the muscle, which like the contraction proper, is primarily independent of oxygen and is included in the first phase. I shall deal first with this phase of activity.

Early in his studies Hill demonstrated a fact which yields an important point in the evidence. Between the mechanical tension which appears in the muscle and the production of heat there is always a direct proportionality. Alike in the steady anærobic metabolism of the quiescent muscle, or during stimulation, or in various forms of rigor mortis however rapidly induced, the appearance of a given quantity of acid is associated with the evolution of a proportional quantity of heat. A specially accurate quantitative proof of this was given by the work of R. A. Peters[8] at Cambridge. Using admirable technique, he showed that while the indirect stimulation of muscle to fatigue involved the evolution of 0.9 calories per gram of tissue, the subsequent induction in the same muscles of rigor by chloroform added 0.89 cals. per gram. When rigor was directly induced in fresh muscle the heat production amounted almost exactly to the sum of the above, and double the heat of fatigue, namely 1.70 cals. Now Fletcher and I had shown, as already mentioned, that in rigor the average production of lactic acid is about double the production in fatigue, and this Peters confirmed. Each gram of acid when it appears in muscle is accompanied by the appearance of about 450 calories and the constancy of this ratio under such different conditions shows that acid and heat owe their origin to one and the same process. Equally important in the development of the views I am putting before you is the indication supplied by such results that the events which give rise to lactic acid formation during normal activity are in no sense of

a different order from those which are responsible for the appearance of the acid during the anærobic metabolism of rest, or in rigor however produced or accelerated.

These results have been in all essentials amply confirmed by the very recent work of Meyerhof,[9] to which in other connections I shall have to make frequent reference.

His experiments have an advantage over the earlier ones in that the estimations of heat and lactic acid were made upon the same set of muscles, and the comparison was direct. At the same time it must be remembered that only micro-methods could be used for such a purpose. Meyerhof found, as the result of change in conditions such as the temperature at which the muscles are stimulated, certain variations in the heat evolved per unit of lactic acid produced but proved that the relation was essentially of the same order as that assumed by Hill and Peters. With regard to the effect of temperature, Hill has very recently shown that in the response to a single shock the relation is the same at all temperatures. In prolonged stimulation it varies. For average conditions we shall be close to the mark of we take, with Meyerhof, 400 small calories as the heat production which is normally associated with formation of 1 gram of lactic acid.

Lactic acid is related in a similar quantitative way with mechanical changes in the muscle. To get clear on this point we must realize certain properties of the muscle as a machine which have been brought fully to light by the investigations of Hill. Earlier experiments had shown that the actual work performed by a contracting muscle bears very variable and apparently accidental relations to the heat evolved. The case is different, however, if we deal with the primary mechanical event which follows immediately upon stimulation and precedes any performance of work. This is a sudden increase of tension in the fibres which can be accurately measured. It means that the elasticity of the fibres has suddenly changed, and its occurrence implies a sudden conversion of chemical potential energy into mechanical potential energy. The subsequent developments in the muscle depend upon the circumstances in which it is placed. If it be free to contract, then part of the energy of the new tensile stress

will appear as work and part, of course, as heat. If the muscle after stimulation cannot contract the whole appears as heat. Hill has established the important fact that the heat evolution is then always proportional to the amount of tension previously established in the muscle. Much, I may say here, that what is quantitative in our present knowledge is due to Hill's recognition of the importance of studying the dynamics of the isometric contraction. Such studies have yielded proof of the relation just mentioned.

Since the mechanical potential energy established in the isometric muscle by stimulation degrades into a proportionate amount of heat, and this heat has been shown to be proportionate under all circumstances to the lactic acid produced, it follows that the original mechanical potential is proportionate to acid production. This Meyerhof has directly shown by estimating the integrative effects of a series of isometric contractions carried on to the point of fatigue. He found that the total mechanical effect is in general proportionate to the total acid formed, the absolute value of each varying with such factors as the nutrition condition of the animals used.

The relations just discussed compel the belief that acid production, the development of tension, and the heat which ultimately leaves the muscle, are all essentially due to one event, and that a chemical change following immediately upon excitation. Here clearly we reach a standpoint, based upon quantitative data, of the utmost importance for the understanding of the dynamics of muscle.

Our next desire will naturally be to discover the nature of the primary chemical reaction concerned. We need then first to know what is the precursor of the lactic acid. All the probabilities would point to carbohydrate as the ultimate, if not the immediate, source of the acid; but the experimental evidence supposed to bear on the matter seemed for a long time hopelessly confused. It is not necessary to enter into the history of controversy on the point. Much of it has been due to the fact that the data upon which arguments have been based were yielded by unsatisfactory methods and so were contradictory

and without quantitative value. Recent work and especially that of Parnas and Meyerhof shows at least that whenever lactic acid appears in muscle an equivalent quantity of carbohydrate disappears. These observers used micro-methods for their estimation, though their methods were carefully controlled. In my laboratory we have recently repeated work upon this point using similar methods upon larger quantities of material. We have been impressed by the exactness with which the amount of lactic formed under any circumstances corresponds with the carbohydrate disappearing.

Seeking detail as to the exact nature of the precursor we may pass at once to the results of the patient investigation of the Frankfort School. Doubtless, having in view the classical discovery of Harden and Young, who showed that in the chemical breakdown of sugar by yeast juice the synthetic formation of a phosphoric ester of hexose is an invariable event, and also being aware of certain data in the literature which suggested that during the activity of muscle inorganic phosphates may be increased at the expense of phosphates organically bound, Embden and his colleagues, Laquer and others, set themselves to look for hexose phosphate in muscle.

The final outcome of a patient and laborious investigation was the proof that this hexose phosphate does undoubtedly exist in muscle and shares in the processes of change.[10] Moreover, mucle-extracts and other tissue-extracts, while quite incapable of converting free sugar into lactic acid, break down the hexose phosphate in such a way as to yield simultaneously both lactic and prosphoric acids. The view may be taken, and if true, it is one of great interest, that the association with phosphoric acid in some way makes easier that intramolecular shift which is involved in the production of lactic acid from dextrose. We can hardly doubt therefore that between the glycogen and the lactic acid of muscular metabolism this combination of sugar with phosphoric acid is an intermediary. It is probably the immediate precursor of the latter and is in any case a precursor at some stage in the processes of production. Its properties justify the title 'lactacidogen' which Embden has applied to it.

In their more general aspects the occurrences of the active phase of a muscle act may be pictured as follows: As the result of stimulation, sugar, originally derived from the glycogen stores, but situated in some position of advantage in the muscle structure and almost certainly combined there with phosphoric acid, suffers a sudden breakdown yielding lactic acid. As a result of this chemical event, preceded, it may be, by a translocation of some pre-existing lactic acid, the muscle elements suffer a marked change in respect of their elastic properties, and this leads to a development of mechanical tension within them proportionate in amount to the acid produced. This tension may then be converted into work; but in such conditions as those which exist when a muscle contracts isometrically, it is wholly degraded into heat. This heat, though by no means to be thought of as identical with the heat of the initial chemical reaction, is always proportionate to the extent of that reaction, and so also to the lactic acid produced. So long as the events of the next phase—the recovery phase—are for any reason in abeyance the acid accumulates in the muscle. These events, in which the influence of oxygen is dominant, must be now considered.

The recovery period is most easily pictured when conditions sharply demarcate it in time, as when a muscle properly supplied with oxygen is engaged in a series of single contractions. It then intervenes between relaxation and the following contraction. But the evidence shows that the chemical processes involved in it, so long as oxygen is fully available, continuously play their part in the chemical equilibrium of muscle, whether quiescent or active.

The facts already discussed have shown that the main event during recovery is the disappearance of lactic acid. But the precise mechanism of its removal is a matter vital to our understanding of the dynamics of muscle. If for instance we endeavor to take the simplest view of the situation and, in analogy with what has been taught concerning plant respiration, conceive that the sequence of events is merely that of acid production during activity, followed by complete combustion of the acid, during recovery, we meet at once an inherent difficulty which has pre-

vented many in the past from recognizing in lactic acid a normal product of activity.

The demands of a working mechanism such as muscle are somewhat different from those of more quiescent plant tissues. It calls not only for a supply of available free energy but for the delivery of this at the right moment.

Now in the breakdown of carbohydrate to yield lactic acid a very small fraction, perhaps one-fortieth, of the chemical potential of the former is made available as free energy. The rest would be set free during the subsequent combustion, but as the act of contraction has *ex hypothesi* preceded this, the natural conclusion would be that the mechanical activity receives no support from oxidations, which then would provide heat alone.

Under such circumstances the consumption of material necessary to yield a given amount of work would be out of all proportion greater than what is known to occur in the normal intact animal.

If then the splitting of carbohydrate into lactic acid as a source of energy for the contraction be no abnormal process, vastly uneconomical, to which the muscle is merely driven by deprivation of oxygen; if the sequence of events we are picturing be real; then, in some way, energy must somehow be made available for activity during what we have called the Recovery Phase. Recent research has made it clear that there is a real post-contractile return of material and energy to the system of the muscle. The facts are of great interest and would seem to bear not alone upon the dynamics of muscle but no less perhaps upon the nature of the relations between oxygen and living processes in general.

During our work upon lactic acid, Fletcher and I obtained an experimental result which seemed to us significant. We submitted muscles to processes of alternating fatigue and recovery, repeated many times. As during each period of recovery lactic acid left the muscles, it is clear that the treatment referred to, if it involve complete oxidation, must ultimately have made a heavy drain upon the sources of the acid. Organs so treated might be expected to show signs of consequent deficiency in these.

Yet when they were warmed to 40°C as to obtain from them Ranke's "heat maximum" it was found that they yielded just as much lactic acid as perfectly fresh unfatigued muscles. Though we tried not to dogmatise upon the matter, we thought that here was some justification for believing that the acid was, during the recovery periods, not burnt away, but perhaps rebuilt; not, of course, with the oxygen into an *inogen,* but into whatever substance had first yielded the acid anærobically. It was afterwards shown however, by Lacquer, that a simpler explanation for the facts is available. The production of lactic acid of muscle is a self regulated reaction stopping short when a certain maximum is reached. If therefore the original supply of precursor is relatively large we need not expect that its partial exhaustion will appreciably reduce the final maximum. There are certain considerations to suggest that the experimental result described is not entirely to be explained in this way; but I need not dwell upon them because there is now other and more direct evidence to show that the processes of recovery reverse the processes of fatigue.

Quite early in his researches Hill measured the heat given out in the period which follows a single muscular contraction, and found that this so called Heat of Recovery to be quantitatively of the same order as the Heat of Contraction. To this result he applied the following argument: The lactic acid produced in contraction disappears during recovery and since the heat associated with the formation is known to be about 400 cals. per gram, while the heat or recovery is about the same, only some 400 cals. can be evolved during the removal of 1 gram. But the total heat of combustion of 1 gram of lactic acid is something like 3,700 cals. It is impossible, therefore, that more than a fraction of the acid which is removed during recovery can be actually burnt. Most of it must be removed in some other way; as Hill thought, by reconstruction into a substance of higher potential energy.

But, before the argument can be completed, more precise and direct information is wanted as to how much material is actually oxidized in the recovery phase. This is not necessarily measured

by the heat given out. It can be determined, however, by measuring the amount of oxygen consumed, especially if at the same time we get to know the respiratory quotient. Such a determination was first made by Parnas[11] in the course of work begun at Cambridge. Parnas found, first of all, that the oxygen consumption of an excised muscle, resting, but previously fatigued and therefore loaded with lactic acid, was definitely greater than that of a fresh resting muscle containing at most a minute quantity of acid. His results seemed to show that this excess in the oxygen consumed corresponded with some exactness to the combustion requirements of the amount of lactic acid known to have disappeared from the fatigued muscle by the end of the experiment. But he found also, and here he demonstrated a point of great importance, that the heat actually evolved was considerably less than what this combustion would produce; the former being indeed only half the latter. Parnas drew from his results the conclusion that while the lactic acid was not resynthetised, but wholly burnt, the energy of its combustion was not all lost to the muscle. On the contrary, a moiety of this energy is by some unknown means employed in restoring potential to the contractile system.

You will not deny that this return of energy to the physical mechanism under the influence of oxygen is a significant event. Its occurrence has been confirmed by the later work of Meyerhof.

In a series of papers which have appeared during the last year, this author, who had previously identified himself with productive studies of general tissue-respiration, has made important contributions to the subject of this lecture. Much of his work constitutes a confirmation of that of Fletcher and myself, as also that of Hill and Peters; though; especially in connection with the effect of conditions on lactic acid formation, he has added precision to details. But he has also added facts, and especially one fact of great importance.

Meyerhof repeated Parnas's experiments on the oxygen consumption of the recovery period, estimating directly in the lactic acid which disappears. The conclusion that part of the energy arising from the oxidation is retained in the muscle was confirmed, but Meyerhof's results differed quantitatively from those of Parnas, and the difference modifies the interpretation of the

facts. Meyerhof agrees with Hill in finding that the observed heat of recovery is of the same order of magnitude as the heat of contraction, though his results suggest that the former is somewhat the greater, in the ratio, say, of five to four. He finds with Parnas that this value is considerably less than what would correspond with the lactic acid (or carbohydrate) burnt; but the figures he obtained for oxygen consumption indicate that not the whole, but no more than one-third to one-fourth, of the lactic acid is actually burnt; the remainder disappears without oxidation. This was Hill's view. But Meyerhof has gone beyond previous observers by showing what this disappearance means. The balance of the acid he finds is actually reconverted into glycogen.

E. J. Lesser,[12] several years ago, showed that the glycogen of intact frogs was greatly reduced as the result of a comparatively brief deprivation of oxygen, and that when the animals were returned to normal respiratory conditions without receiving food the total glycogen returned in part to its original value. This might possibly indicate a resynthesis from lactic acid formed during the anoxybiosis. But the process in the whole animal might have been quite indirect, and involve other organs than the muscles. Meyerhof on the other hand, by simultaneous estimations of lactic acid and glycogen in excised muscles, before and after their recovery in oxygen from previous fatigue, has shown directly that during the process the one is actually reconverted into the other.

Meyerhof's results have been fully confirmed in my laboratory by the conjoint work of Miss D. Foster and Miss Moyle.

Energy, it would seem is returned to the muscle along two lines; one involving a restoration of chemical potential, and the other the restoration of potential to a physical system. Each event has its own importance in the return to the status quo ante.

From the chemical standpoint the equilibrium changes involved during activity and recovery resolve themselves ultimately into the simple reversible equation:

$$\text{Glycogen} \rightleftharpoons \text{Lactic acid}$$

So long as anærobic conditions prevail the production of lactic acid is an irreversible process; under the influence of oxygen it

becomes reversible, though at the cost of the oxidation of a part (say one-fourth) of the reacting materials.

We may provisionally put the relations just discussed into quantitative form with the data of Hill and Meyerhof as a basis. Calculated as for one gram of muscle the average of Meyerhof's results gives for the heat of contraction 0.75 cals; for that of recovery 1.0 cals; and for the heat of the lactic acid (or carbohydrate) actually burnt during recovery 1.75 cals. If we calculate in round figures the calories corresponding to one gram of lactic acid either produced or removed we get the data in a convenient form:

Heat of anærobic contraction	Heat of recovery in oxygen.	Total heat of activity in oxygen.
400 cals.	500 cals.	900 cals

Heat of combustion of materials burnt.

900 cals.

This is a balance sheet which any Auditor would pass as satisfactory. The heat lost as a result of an exothermic change during the fatigue phase (400 cals.) is balanced by the absorption of an equal amount of heat due to an endothermic change during the recovery phase. On the other hand the heat of combustion of materials actually shown to have been oxidized exactly provides the total loss of energy (900 cals.) during the whole cycle of change. As a result of the recovery processes, therefore, the muscular system is restored to the condition which existed before activity, except for the fact that, in the disappearance of part of its glycogen store, it has lost chemical potential energy equivalent to the energy it has expended.

Although at this stage we have arrived on solid ground it is clear that the mind cannot be satisfied to rest upon it without some attempt to visualize from a somewhat new and better standpoint the actual mechanism of muscular contraction. But the view ahead is not yet wholly clear and much must still be left to the imagination; though we have less reason than before to

indulge in theories of contraction which are wholly speculative. To this extension of the subject I can here contribute little. My own ostensible task is indeed nearly finished for I have now exhausted the available facts of a strictly chemical nature.

A few words may be said, however, in an attempt to relate these facts rather more clearly to the mechanical changes in muscle, premising that we at once enter a region of hypothesis. It is clear at any rate that we must dismiss all thought of the muscle as a heat engine. It works directly with chemical energy, taking especial advantage at some stage in a sequence, of the surface forces which its structure enables it to develop. The heat production is largely if not entirely irreversible. I need not press this claim. It is inherent in all that has been said, and you have an easily accessible statement supporting it in the Presidential Address delivered to the Society of Biological Chemists in 1913. The recently won facts affect but little the general arguments used by Professor Macallum on this occasion.

It is very important to remember here that the work of Hill has confirmed in a highly quantitative way the statement of Blix that the amount of tension developed in a muscle depends upon the extent of the available surfaces. Hill has shown that the quantity of energy set free upon stimulation is directly proportional to the length of the fibres and not to the volume of the muscle; a relationship which was also found by Patterson and Starling to hold for the ventricular contraction of the heart. The prime chemical event would seem to occur at a boundary between two phases in the muscle structure.

That the appearance of lactic acid (hydrogen ions) on the surface may be the efficient cause of the change of elasticity was urged by Mines when he was working at Cambridge some years ago, and I think the view is very generally though not universally accepted. The primary happening on contraction would seem to be clear. It consists in the sudden appearance of acid at a particular surface with the consequent development of tension. This does not necessarily mean that the breakdown of carbohydrate which yields the acid is quite so sudden, for there is a possibility not yet dealt with to which I must refer. Hill's most

recent work has involved a closer analysis of the heat given out on a single contraction, and also a comparison of that which appears on very brief stimulation with that produced during more prolonged stimulation. He concludes from his results that within some closed location in the quiescent structure carbohydrate and lactic acid are in equilibrium; there exists, so to speak, somewhere, a certain pressure head of the acid before contraction occurs. The first effect of a stimulus is to affect the permeability of the containing structures and lactic acid passes to the locus where it is effective in producing contraction. This result follows upon the briefest of stimuli; it also happens at the earliest stage of every stimulus

$$[\text{Carbohydrate} \rightleftharpoons \text{Lactic acid}]^2 \longleftarrow$$

If the stimulation is prolonged beyond this point, what I have called the pressure head of lactic acid disappears, and the continued production of lactic acid necessary for the maintenance of tension depends now on the steady progress of the reaction

$$\text{Carbohydrate} \longrightarrow \text{Lactic acid.}^*$$

The conceptions just put forward are due to Hill. They are hypothetical, but they are supported, as I have said, by his latest analysis of the heat phenomena. The heat produced by a very short maximal stimulus and that evolved at the earliest period of any maximal stimulus is constant no matter what the external temperature. The process with which it is associated has therefore no temperature cœfficient and is represented by that sudden diffusion of preformed lactic acid of which Hill has conceived. If the stimulus be prolonged the later heat formation rises with the external temperature because we have now to deal with the temperature cœfficient of the reaction which continues to produce fresh lactic acid.

Part of the heat evolved during what we have agreed to call the active or fatigue phase is associated, as Hill has now also shown experimentally, with relaxation. What kind of event gives rise to it? If contraction follows upon the appearance of acid at certain effective surfaces, relaxation will follow upon its leaving

* The intervention of the hexose phosphate is here omitted for the sake of simplicity.

those surfaces. But relaxation precedes the recovery phase and occurs without oxygen. What then removes the acid from the contractile surface? Having reached a certain local concentration it will certainly tend to diffuse away into places of lower concentration, and unless, as during continued stimulation, the concentration is maintained at the contractile surface. relaxation may be expected, at some moment or other, to follow. Meyerhof takes the view that diffusion is indeed the sufficient cause of relaxation and considers that the heat of the relaxation is accounted for by the effect of diffusing acid upon the colloids of the muscle plasma. Hill, on the other hand, postulates a more definitely chemical event at this point and bases his view upon the fact that he finds a high temperature cœfficient for the relaxation process. There are difficulties I feel in either view. The heat given out during relaxation forms, as Hill and Hartree have shown, a large proportion of the total heat of the fatigue phase. It is difficult to understand this upon Meyerhof's view; and even if we agree with Hill in thinking that the acid which has initiated contractions is, so to speak, inactivated by the formation of some fresh compound, it is hard to picture what type of compound this might be. Doubtless simple neutralization by the carbonates of the muscle plasma plays a part here, but it seems to be a small one. If some other compound is formed it would seem to have a high heat of formation, and yet it must be some loose compound; for, after all, it is lactic acid itself which analytical methods extract from fatigued muscle. The process of relaxation is not yet, I think, fully understood.

The significance of oxidation in the recovery phase is much more easily grasped. Whatever the condition of the lactic acid at the end of the fatigue phase it is easy to see that its oxidative removal is an important factor in the preparation for the next contraction. If the acid during relaxation diffuses from the contractile surfaces into adjacent elements of the muscle structure then in the absence of the oxidative removal, the diffusion gradient would get less and less; acid would therefore tend more and more to accumulate at the surfaces and relaxation would become increasingly incomplete as we know it does during the progress

of fatigue. On Meyerhof's view an important consequence of the recovery processes is the restoration of the diffusion gradient for the translocation of acid. On Hill's view the events would have just the same significance; for oxidation of the combined lactic acid will prevent the saturation of whatever substance it may be supposed to combine with.

In any case we see that the function of oxygen in the life of muscle is not to provide directly the energy of its specific physiological activity. It rather restores potential when it has run down, and clears the mechanism so that the actual sources of energy can be efficiently drawn upon.

We shall not, however, understand the whole of the fascinating chemical system which has occupied our attention if we think only of its energy exchange, and the material events which support them.

All the Dynamic phenomena we have considered, though they may be displayed to perfection for long periods by muscles excised from the body, are of course displayed only while a certain equilibrium is maintained among a complicated set of factors; the equilibrium which is associated with, and necessary for, the property of irritability.

So long as this is maintained, or, if lost, is capable of restoration, so long are we justified in attributing life to the tissue. A moment comes when the necessary equilibrium is no longer maintained, and this moment is usually—though, as we are to see, not always—associated with, and marked by, a happening which seems to have a more or less critical character—the rigor of death. This may arise, even in quiescent muscle, as the final result of oxygen lack alone; but we have learnt to make no sharp distinction between the onset of rigor mortis and that gradual progress of fatigue which in active muscle may lead up to it; a progress which is accelerated by deprivation of oxygen and delayed by a proper oxygen supply.

It is the accumulation of products of change and not the exhaustion of supplies of oxidizable material which leads to fatigue and ultimately to death in rigor. Fletcher's early work and the work we did together as well as such observations as

those of Joteyko left little doubt that the prime if not the sole cause of fatigue, and, no less, of death in rigor, is the accumulation of lactic acid. Both phenomena are due to the effect of this upon the colloid machinery of the muscle. Fatigue increases as the accumulation increases and the critical moment of rigor mortis (in so far as it is critical) corresponds with the attainment of a certain concentration of acid.

These are the common and obvious events. When they occur they overshadow other failures in equilibrium which may nevertheless be as fatal to what we call the life of the tissue. An excised amphibian muscle when quiescent in an atmosphere of oxygen does not accumulate lactic acid, and never displays rigor mortis at all. Yet though it lives surprisingly long it is certainly not immortal. It ultimately ceases to be irritable and we must then speak of its death; but it is death without rigor. What now is the cause of death? Miss D. L. Foster and Miss D. M. Moyle have carried out in my laboratory some experiments which bear upon the answer to this question and the results seem to be of great interest.

If frogs' limb muscles are kept in oxygen at 0°C they remain irritable for periods which vary with the season from about a fortnight to three weeks. The irritability declines relatively fast immediately after the first few days, then remains constant for a period, and later declines more rapidly to zero. But the muscles when, finally, they fail entirely to respond to the strongest electrical stimulus show no signs of rigor mortis. In their flaccidity and in their general appearance they resemble perfectly fresh muscles. Corresponding with this they are found to contain only that original "resting minimum" of lactic acid which must have been present when they were originally removed from the frog. In parenthesis it may be stated that this failure to accumulate lactic acid is not due to the complete inhibition by the low temperature of the chemical processes concerned. In nitrogen the muscles at 0°C accumulate lactic acid at a steady rate, a circumstance which is associated with a much earlier loss of irritability. Its failure to accumulate is still the effect of oxygen. But the remarkable fact is that wholly non-irritable

muscles may be essentially intact in respect of their chemical mechanism. Whatever stimulates chemical change in a normal muscle stimulates the same change in muscles which have lost irritability during exposure to oxygen, though throughout all stimuli fail to produce a mechanical response. If kept at 40°C their glycogen is converted into lactic acid with a normal rapidity and the usual maximum is reached. If exposed to chloroform vapor the usual chemical response is seen. If chopped up the usual acceleration of lactic acid production is displayed. It is noteworthy, moreover, that though when electrically tested they show no current of action, transmitting no diphasic change of potential, they yet display a demarcation current as another indication of their chemical integrity. By chemical criteria we should say they were alive, electrical stimulation decides they are dead. These would seem to be a dislocation in the normal sequence of stimulation and energy discharge. Can we picture any physical basis for such a dislocation? I would offer a provisional view: Nernst's theory of excitation as extended by the work of Lucas and Adrian at Cambridge postulates the free movement of ions. The attainment of a certain concentration of these upon a surface or surfaces within the tissue determines the condition of excitation. Now in an isolated system containing colloids and dissolved electrolytes there is a tendency with flux of time towards an increase of stability in the relations which exist. Ions which start free gradually form relatively stable association with the colloids. This, I would suggest, is what occurs when the muscle gradually loses irritability under the conditions described. During the long survival period in oxygen at 0°C there is none of that clogging of the machinery with metabolic products which ordinarily precedes the death of the tissue, but there is a gradual immobilization of ions. This makes impossible that movement towards an efficient concentration at a surface which is postulated in the Nernst theory of excitation. An examination of the osmotic properties of the unfatigued yet non-irritable muscles supports this view. Though the actual loss of material which they have suffered during their survival life in oxygen consists solely of a small proportion of their glycogen store, the osmotic pressure in

the fibres is markedly lower than that observed in muscles freshly removed from the body. The living condition demands the maintenance of a proper equilibrium in the Colloidal apparatus of a tissue as well as the continuance of chemical reactions which proceed in that apparatus. The nature of the apparatus plays doubtless an important part in the organization of the reactions, and it is necessary to study them together.

Much doubtless has to be learnt before the total activities of the contractile tissues can be fully described in terms of Physics and Chemistry, but I think that the knowledge already won with which I have dealt very partially, should encourage the belief that the essential phenomena involved are far from elusive. If the biochemist duly respects his materials while he applies quantitative methods to their study he need not be dismayed by the circumstance that they are only interesting when alive.

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